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(54) **Pyraxolidinone CCK and gastrin antogonists and pharmaceutical formulations thereof.**

(57) Novel substituted pyrazolidinones have been found to exhibit significant binding to cholecystokinin (CCK) receptors and gastrin receptors in the brain and/or peripheral sites such as the pancreas, stomach, and ileum. The pyrazolidinones are CCK and gastrin receptor antagonists and find therapeutic application in the treatment of gastrointestinal disorders, central nervous system disorders and for appetite regulation in warm-blood vertebrates. Pharmaceutical formulations for such indications are described.

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This invention relates to biologically active pyrazolidinones. More particularly, this invention is directed to certain substituted pyrazolidinones which bind to receptors for cholecystokinin (CCK), e.g., those of the brain and pancreas, and to receptors for gastrin, e.g., those of the stomach. The compounds are CCK and gastrin antagonists and are useful in the treatment and prevention of CCK and gastrin-related disorders of the gastrointestinal, central nervous and appetite regulatory systems of warm-blooded vertebrates, especially humans.

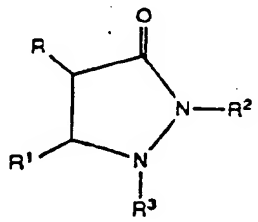
Cholecystokinin (CCK) is a neuropeptide found in both gastrointestinal tissue and the tissues of the central nervous system. CCK is believed to play an important role in appetite regulation. Among the effects of CCK are stimulation of colonic motility, stimulation of gall bladder contraction, stimulation of pancreatic enzyme secretion, and inhibition of gastric emptying. CCK reportedly coexists with dopamine in certain mid-brain neurons and thus may also play a role in the functioning of dopaminergic systems in the brain. Gastrin is a neuropeptide found particularly in the gastrointestinal tract. It is one of the primary natural stimulators of gastric acid secretion. It also has growth stimulatory effects on a variety of gastrointestinal tissues.

CCK and gastrin antagonists are useful in the treatment and prevention of CCK and gastrin-related disorders of the gastrointestinal and central nervous systems, as well as modulation of the appetite regulatory systems of warm-blooded vertebrates. The CCK/gastrin receptor family is thought to contain three receptor subtypes, for which the location of the prototype receptor is given in parentheses: CCK-A (pancreas), CCK-B (brain), and gastrin (stomach fundus).

Several classes of CCK receptor antagonists have been reported in the literature. One class comprises derivatives of cyclic nucleotides, for example, dibutyryl cyclic GMP. Another art recognized class of CCK antagonists comprise the C-terminal fragments and analogs of CCK. Another class of CCK receptor antagonists are amino acid derivatives including proglumide, a derivative of glutaramic acid, and the N-acyltryptophanes such as p-chlorobenzoyl-L-tryptophan. More recently certain substituted amino phenyl compounds were described as CCK antagonists in published European Patent Application 0166355. Because of the wide range of potential clinical applications of CCK binding compounds, intensive research efforts have been ongoing to define other compounds exhibiting CCK receptor binding properties.

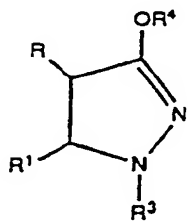
This invention is directed to novel pyrazolidinone compounds of Formula I or II below which have been found to exhibit CCK and gastrin antagonist activity. These compounds are useful in the treatment and prevention of CCK-related disorders of the gastrointestinal and central nervous systems, as well as in modulating the appetite regulatory systems of warm-blooded vertebrates, especially humans. As gastrin antagonists, they are particularly useful in the treatment and prevention of gastrointestinal ulcers, and of neoplasms of gastrointestinal origin.

This invention is directed to compounds of the formula



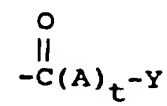
I

or



II

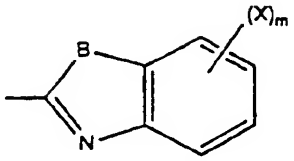
wherein R and R^1 are independently hydrogen, C_1-C_6 alkyl, phenyl, benzyl, naphthyl, pyridyl or substituted phenyl having 1, 2, or 3 substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halo, trifluoromethyl, phenyl, phenoxy, phenyl(C_1-C_4 alkyl), phenyl(C_1-C_4 alkoxy), phenylacetyl, C_1-C_6 alkanoyl, cyano, carbamyl, nitro, C_1-C_6 alkoxy-carbonyl, methylenedioxy, C_3-C_6 alkylene, amino, -NH(C_1-C_4 alkyl or benzyl), and N(C_1-C_4 alkyl)$_2$; R_2 is hydrogen, C_1-C_6 alkyl, carboxymethyl, C_1-C_4 alkoxycarbonylmethyl or a group of the formula



wherein t is 1 or 0; A is -CH_2-, -O-, -NH- or -N(C_1-C_6 alkyl)-; and Y is phenyl or substituted phenyl as defined above;

R_4 is C_1-C_6 alkyl, carboxymethyl, or C_1-C_4 alkoxycarbonylmethyl;

R_3 is hydrogen or a group of the formula



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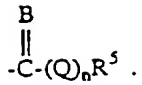
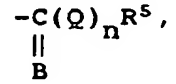
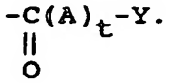


wherein B is O or S; X is selected from the phenyl substituents defined above; m is 0, 1 or 2; n is 0 or 1; Q is -NH-, -N(C_1-C_6 alkyl)-, -S-, or -O-; and R^5 is a group of the formula -[CH(R^6)]$_q$-(CH_2)$_r$-R^7 wherein R^6 is hydrogen or C_1-C_6 alky; q is 0 or 1; r is 0, 1 or 2; and R^7 is hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, pentafluorophenyl, pyridyl, tetrahydronaphthyl, indolyl, quinolinyl, phenyl, naphthyl, or phenyl or naphthyl substituted with 1, 2, or 3 substituents as defined above for phenyl; or the group -(Q)$_n$$R^5$ is 2-tetrahydroisoquinolinyl; and the pharmaceutically acceptable salts thereof;

provided that at least one of the groups R or R^1 is other than hydrogen or C_1-C_6 alkyl, and R or R^1 is hydrogen only when the other of R and R^1 is substituted phenyl in which the substituent is phenyl; and provided further that at least one of the groups R_2 and R_3 is other than hydrogen, and when R^3 is a group of the formula



R^3 is other than a group of the formula



In the compounds of Formula I or II, the groups R and R^1 can be in either the cis or trans configuration relative to the plane of the pyrazolidinone ring. The trans configuration, preferred in accordance with the present invention, is indicated to be the thermodynamically favored form.

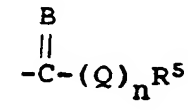
As used herein "halo" refers to fluoro, chloro, or bromo. The term "C_1-C_6 alkyl" includes both straight and branched chain alkyl and cycloalkyl and includes methyl, ethyl, propyl, cyclopropyl, isopropyl, butyl, methylcyclopropyl, cyclobutyl, isobutyl, t-butyl, pentyl, cyclopentyl, neopentyl, hexyl, cyclohexyl, 2-methylpentyl and the like. In the "C_1-C_6 alkoxy" and "C_1-C_6 alkylthio" substituents, the alkyl portion is C_1-C_6 alkyl as defined above. The term "C_1-C_6 alkanoyl" includes formyl, acetyl, propionyl, butyryl, pentanoyl, hexanoyl, and the like.

The term "pharmaceutically acceptable salts" encompasses those salts that form by standard acid-base reactions with basic groups (such as amino groups) and acidic groups, particularly carboxylic acid groups, on the compounds of Formula I or II. Thus, the pharmaceutically acceptable salts of the present invention can be prepared by conventional chemical methods from the compounds of Formula I or II which contain a basic or acidic moiety. Generally, the salts are prepared by reacting the free base or acid with a stoichiometric amount or with an excess of the desired salt-forming acid or base in a suitable solvent or combination of solvents. Suitable salt-forming acids include inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, citric, malic, tartaric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethanedisulfonic, oxalic, benzenesulfonic, picric, cinnamic, and like acids. Bases which find use for preparation of salts of compounds of Formula I or II having an acidic moiety include alkali or alkaline earth metal hydroxides such as sodium, potassium, lithium, calcium, or magnesium hydroxides, ammonia, or organic bases such as benzylamine, dibenzylamine, dibenzylethylenediamine, triethylamin , trim thylamine, piperidine, pyrrolidine, 2-hydroxyethylamine, bis(2-hydroxyethyl)amine, phenylethylbenzylamine, and like organic amines.

The compounds of this invention bind to CCK and gastrin receptors in the brain and/or peripheral sites such as the pancreas, gall bladder, stomach, and ileum. Their ability to antagonize CCK and gastrin makes these compounds useful as pharmaceutical agents for the treatment and prevention of disease states wherein CCK or gastrin may be involved, for example, gastrointestinal disorders such as irritable bowel syndrome, ulcers,

excess pancreatic or gastric secretion, acute pancreatitis, motility disorders, neoplasms of gastrointestinal origin, central nervous system disorders involving CCK's interaction with dopamine, such as neuroleptic disorders, tardive dyskinesia, Parkinson's disease, psychosis or Gilles de la Tourette Syndrome, other CNS disorders where CCK is believed to be a causative factor, such as panic attacks and other forms of anxiety, and in modulating appetite regulatory systems.

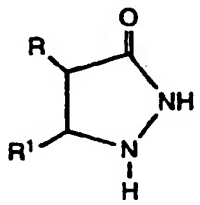
Preferred CCK and gastrin receptor binding compounds of this invention are the pyrazolidinones of Formula 1, particularly those wherein R and R^1 are in the trans configuration relative to the plane of the pyrazolidinone ring. Preferably, R and R^1 are phenyl or substituted phenyl. A preferred group of compounds of Formula I are those wherein R^2 is hydrogen and R^3 is a group of the formula



One series of such preferred compounds of this invention are those wherein B is sulfur, n is 1, Q is -NH-, and R^5 is phenyl or substituted phenyl.

Another preferred group of compounds exhibiting a consistent pattern of significant binding to CCK and gastrin receptors are those compounds of Formula I wherein R^2 is hydrogen and R^3 is a moiety defined by the group $-CONH-[CH(R^6)]_q-(CH_2)_r-R^7$. Especially preferred of those compounds are those wherein q and r are 0 and R^7 is phenyl, substituted phenyl, 2-naphthyl or 3-quinolinyl and R and R^1 are phenyl, naphthyl, or substituted phenyl in the trans configuration relative to the plane of the pyrazolidinone ring. When R^7 is substituted phenyl, preferred substituents are halo, more particularly, chloro, bromo or iodo; trifluoromethyl; C_1-C_4 alkyl; C_3-C_4 alkylene; benzyloxy; and methylthio.

The compounds of this invention are readily prepared from the corresponding compounds of the formula



III

The intermediate 3-pyrazolidinones are readily prepared by reacting hydrazine with the corresponding α,β-unsaturated esters of the formula R^1-CH=C(R)-COOR′ wherein R and R^1 are as defined above and R′ is an ester forming group, typically C_1-C_6 alkyl. The present compounds are prepared generally by acylating or alkylating the 3-pyrazolidinones of Formula III under neutral or basic conditions with acylating or alkylating agents selected to give the targeted compound of this invention.

In another embodiment of this invention there is provided pharmaceutical formulations comprising as an active ingredient an effective amount of a compound of Formula I or II and a pharmaceutically acceptable carrier, excipient or diluent therefor. Such formulations can be prepared for oral or parenteral administration for the treatment and prevention of disorders of the gastrointestinal, central nervous and appetite regulatory systems of warm-blooded vertebrates, especially a man.

For oral use of an antagonist of CCK or gastrin of this invention, the selected compound can be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets, common excipients include binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, polyvinylpyrrolidine (Povidone), methylcellulose, ethylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sucrose and starch; fillers and carriers, for example, corn starch, gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid; lubricants such as magnesium stearate; disintegrants such as croscarmellose, microcrystalline cellulose, corn starch, sodium starch glycolate and alginic acid; and suitable wetting agents such as lauryl sulfate. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are desirable for oral use, the active ingredient can be combined with emulsifying and suspending agents, for example, sorbitol, methylcellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel or hydrogenated edible oils, for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; flavoring agents such as peppermint, oil of wintergreen, cherry flavor-

ing or the like; and preservatives such as m thyl or propyl p-hydroxybenzoates or ascorbic acid.

The pharmaceutical formulations in accordance with this invention can also be prepared for parent ral use. Such formulations typically take the form of sterile isotonic solutions of the active ingredient according to standard pharmaceutical practice.

The appropriate dose of the compound of the present invention for its use as an antagonist of CCK or gastrin in humans will vary according to the age, weight and response of the individual patient, as well as the severity of the patient symptoms and the nature of the condition being treated. Thus, the preferred daily dose will normally be determined by the prescribing physician. However, in most instances, effective daily doses of the compounds of this invention will range from about 0.05 mg to about 50 mg/kg and preferrably about 0.5 mg to about 20 mg/kg in a single or divided doses.

The following Examples are provided to describe further the compounds of this invention and methods for their preparation.

Tetrahydrofuran (THF) was dried by distillation from sodium/benzophenone. Reactions and workup steps were conducted at room temperature unless otherwise noted. Solvents were removed using a rotary evaporator at reduced pressure. Chromatography was performed on normal-phase silica columns except as noted. Titrations were performed in 2:1 DMF:H_2O as solvent.

Example 1

1-[(4-Chloro-3-trifluoromethylphenyl)amino-carbonyl]-4,5-diphenyl-3-pyrazolidinone. [Method A]

4,5-Diphenyl-3-pyrazolidinone (3.00 g, 12.6 mmol) was dissolved in 40 mL THF under nitrogen, then a solution of 4-chloro-3-trifluoromethylphenylisocyanate (2.87 g, 13.0 mmol, 1.03 eq.) in 10 mL THF added over 2 min. After 2.3 hr, solvent was removed in vacuo, and the residue triturated with 25 mL toluene. The resulting solid was pulverized, washed twice with toluene, and dried in vacuo at 65°C to give 4.94 g (85%) white solid. ^{1}H NMR (d_6-DMSO) δ 3.81 (br s, 1H), 5.56 (br s, 1H), 7.26-7.50 (m, 10H), 7.62 (d, J=9 Hz, 1H), 7.89 (dd, J=3, 9 Hz, 1H), 8.13 (br s, 1H), 9.64 (br s, 1H), 10.90 (br s, 1H); mass spectra (MS) 460 ($M+1^+$);

Analysis for $C_{23}H_{17}ClF_3N_3O_2$:

Calc.: C, 60.07; H, 3.73; N, 9.14;

Found: C, 59.99; H, 3.60; N, 8.89.

Example 2

1-[(4-N,N-Dimethylaminophenyl)aminocarbonyl]-4,5-diphenyl-3-pyrazolidinone. [Method B]

4-N,N-Dimethylaminoaniline (2.00 g, 14.68 mmol) and triethylamine (3.63 g, 35.87 mmol, 2.44 eq.) were dissolved in 50 mL toluene under nitrogen, then triphosgene (1.45 g, 4.89 mmol, 0.333 eq.) added in one batch as a neat solid. The mixture was heated to reflux for 2.5 hr, cooled, then quickly filtered, the collected solid washed twice with toluene, and the combined filtrates evaporated in vacuo to give crude 4-N,N-dimethylaminophenylisocyanate as 2.57 g brown oil. This was redissolved in 50 mL THF and a solution of 4,5-diphenyl-3-pyrazolidinone (3.50 g, 14.69 mmol, 1.00 eq.) in 50 mL THF added over 3 min. After 20.7 hr, solvent was removed in vacuo and the product isolated by chromatography (preparative HPLC; 0-50% EtOAc:toluene gradient) as 1.73 g yellow oil which slowly crystallized. Recrystallization from toluene gave 744 mg (13%) white crystalline solid:

^{1}H NMR (d_6-DMSO) δ 2.84 (s, 6H), 3.71 (s, 1H), 5.55 (s, 1H), 6.67 (d, J=8 Hz, 2H), 7.12-7.52 (m, 12H), 8.86 (br s, 1H), 10.70 (br s, 1H); MS 400 (M^+); titration pK_a's 4.0, 7.9.

Analysis for $C_{24}H_{24}N_4O_2$:

Calc.: C, 71.98, H, 6.04, N, 13.99;

Found: C, 72.08, H, 6.06, N, 14.06.

Example 3

1-[(4-Benzyloxyphenyl)aminocarbonyl]-4,5-diphenyl-3-pyrazolidinone [Method C]

4-Benzyloxybenzoic acid (2.0 g, 8.8 mmol) was suspended in 50 mL toluene with oxalyl chloride (5 mL) and heated to reflux for 15 min. Solvent was removed in vacuo, the residue redissolved in 30 mL acetone, and an aqueous solution of NaN_3 (1.16 g, 17.6 mmol, 2.0 eq. in 10 mL H_2O) added dropwise with external cooling by a water bath. The mixture was stirred for 1 hour, diluted with H_2O, extracted twice with toluene, then the

combined extracts washed with water and brine, and dried over Na_2SO_4. This solution of acyl azide was treated with 4,5-diphenyl-3-pyrazolidinone (1.6 g, 6.8 mmol, 0.76 eq.), warmed until bubbles evolved, and heating maintained for 30 min. After stirring overnight at room temperature, the solvent was removed in vacuo, and the product isolated by chromatography (0-30% EtOAc:hexane gradient) as 1.6 g (52%) white solid: mp 127-30°C;
^{1}H NMR ($CDCl_3$) δ 3.95 (d, J=6 Hz, 1H), 5.0 (s, 2H), 5.55 (d, J=6 Hz, 1H), 6.8 (d, J=10 Hz, 2H), 6.86-7.46 (m, 16H), 7.05 (d, J=10 Hz, 2H), 8.95 (s, 1H); MS 463 (M^+); titration pK_a 7.7.

Analysis for $C_{29}H_{25}N_3O_3$:
Calc.: C, 75.14; H, 5.44; N, 9.07;
Found: C, 75.15; H, 5.49; N, 9.14.

Example 4

1-[(2-[1,2,3,4-Tetrahydronaphthyl])amino-carbonyl]-4,5-diphenyl-3-pyrazolidinone [Method D]

1,2,3,4-Tetrahydro-2-naphthoic acid (639 mg, 3.63 mmol) was dissolved in 80 mL benzene under nitrogen, azeotropically dried by distilling a small portion of the solvent, then diphenylphosphorylazide (1.12 g, 4.08 mmol, 1.1 eq.) and Et_3N (0.41 g, 4.02 mmol, 1.1 eq.) added and the mixture heated to reflux for 1 hour. Solvent was removed in vacuo, the residue dissolved in dry THF under nitrogen, and 4,5-diphenyl-3-pyrazolidinone (784 mg, 3.29 mmol, 0.91 eq.) added and the mixture stirred overnight. The solvent was removed in vacuo and the product isolated by chromatography (25-50% EtOAc:hexane gradient) as 0.92 g (68%) white foam. Recrystallization of a 120 mg sample from i-Pr_2O:i-PrOH gave 94 mg white solid, containing a 1:1 mixture of two diastereomers by NMR: mp 82-95°C;
^{1}H NMR ($CDCl_3$) δ 1.46-1.66 (m, 1H), 1.79-1.97 (m, 1H), 2.30-2.84 (m, 2H), 2.95 (apparent t of d, J=6, 16 Hz, 1H), 3.87 (apparent d, J=6 Hz, 1H), 4.09 (m, 1H), 5.12 (m, 1H), 5.34 (apparent d of d, J=6, 14 Hz, 1H), 6.86-7.40 (m, 14 H), c. 9.0 (v br s, 1H); MS 411 (M^+).

Analysis for $C_{26}H_{25}N_3O_2$:
Calc.: C, 75.89; H, 6.12; N, 10.21;
Found: C, 75.75; H, 6.32; N, 9.72

Example 5

1-[(3-Trifluoromethylbenzoyl]-4,5-diphenyl-3-pyrazolidinone [Method E]

A solution of 4,5-diphenyl-3-pyrazolidinone (2.0 g, 8.4 mmol) in 50 mL CH_2Cl_2 and 5 mL pyridine was treated dropwise with a solution of 3-trifluoromethyl-benzoylchloride (1.4 g, 8.4 mmol) in 25 mL CH_2Cl_2 and stirred overnight. The mixture was washed with IN HCl, dried over Na_2SO_4, evaporated, and the product isolated by chromatography (preparative HPLC) as 840 mg (24%) purple foam:
^{1}H NMR ($CDCl_3$) δ 3.83 (s, 1H), 5.16 (s, 1H), 7.2-7.64 (m, 15H); MS 410 (M^+); titration pK_a 7.15.

Analysis for $C_{23}H_{17}F_3N_2O_2$:
Calc.: C, 67.31; H, 4.18; N, 6.83;
Found: C, 67.52; H, 4.18; N, 6.66.

Example 6

1-[(4-Chlorophenyl)oxycarbonyl]-4,5-diphenyl-3-pyrazolidinone [Method F]

A solution of 4,5-diphenyl-3-pyrazolidinone (1.25 g, 5.26 mmol) in 50 mL $CHCl_3$ was treated with a solution of 4-chlorophenylchloroformate (1.0 g, 5.26 mmol) in 10 mL $CHCl_3$ and stirred overnight. The solvent was removed in vacuo and the residue recrystallized from EtOAc:hexane to give 1.6 g (58%) white solid: mp 175-7°C.
^{1}H NMR ($CDCl_3$) δ 3.98 (d, J=6 Hz, 1H), 5.62 (d, J=6 Hz, 1H), 6.8-7.5 (m, 15H); MS 392 (M^+); titration pK_a 7.8.

Analysis for $C_{22}H_{17}ClN_2O_3$:
Calc.: C, 67.26; H, 4.36; N, 7.13;
Found: C, 67.49, H, 4.54, N, 7.17.

Example 7

1-[(3,4-Dichlorobenzyl)aminocarbonyl]-4,5-diphenyl-3-pyrazolidinone [Method M]

A solution of 1-[(4-nitrophenyl)oxycarbonyl]-4,5-diphenyl-3-pyrazolidinone (1.00 g, 2.48 mmol) and 3,4-dichlorobenzylamine (5 mL) in 50 mL abs. EtOH was heated to reflux for 8 hours. Solvent was removed in vacuo, the residue taken up in CH_2Cl_2, washed twice with 1N HCl and once with pH 7 buffer, and dried over Na_2SO_4. After removal of solvent in vacuo, the product was purified by chromatography (0-35% EtOAc:hexane gradient) to give 250 mg (23%) solid:
^1H NMR ($CDCl_3$) δ 3.93 (d, J=6 Hz, 1H), 4.28 (dABq, J=7, 15 (JAB) Hz, Δu=48 Hz, 2H), 5.50 (d, J=6 Hz, 1H), 5.56 (br t, J=7 Hz, 1H), 6.92-7.44 (m, 13H), 8.73 (br s, 1H); MS 439 (M^+); titration pK_a 8.4

Analysis for $C_{23}H_{19}Cl_2N_3O_2$:
Calc.: C, 62.74; H, 4.35; N, 9.54;
Found: C, 62.49; H, 4.53; N, 9.25.

Example 8

2-[(4-Chloro-3-trifluoromethylphenyl)amino-carbonyl]-4,5-diphenyl-3-pyrazolidinone [Method N]

1-[(4-Chloro-3-trifluoromethylphenyl)amino-carbonyl]-4,5-diphenyl-3-pyrazolidinone (2.00 g, 4.35 mmol) in 100 mL toluene was heated at reflux for 24 hours. After removal of solvent in vacuo, the rearanged product was isolated by chromatography (CHI_2Cl_2), then recrystallized from i-Pr_2O:hexane, to give 300 mg (15%) white solid: mp 72-4°C.
^1H NMR ($CDCl_3$) δ 4.22 (d, J=12 Hz, 1H), 4.82 (dd, J=9, 12 Hz, 1H), 5.44 (d, J=9 Hz, 1H), 7.20 (m, 2H), 7.32-7.42 (m, 8H), 7.46 (d, J=9 Hz, 1H), 7.72 (dd, J=3, 9 Hz, 1H), 7.87 (d, J=3 Hz, 1H), 10.56 (br s, 1H); MS 459 (M^+).

Analysis for $C_{23}H_{17}ClF_3N_3O_2$:
Calc.: C, 60.07; H, 3.73; N, 9.14;
Found: C, 59.95; H, 3.92; N, 8.88.

Example 9

1-[6-Chloro-2-benzothiazolyl]-4,5-diphenyl-3-pyrazolidinone [Method O]

The reaction was conducted under a dry nitrogen atmosphere. A suspension of 4,5-diphenyl-3-pyrazolidinone (1.19 g, 5.00 mmol) in 35 mL toluene was treated with 0.40 g NaH (60% in mineral oil; hydride content 0.24 g, 10.0 mmol, 2.00 eq.), and the mixture stirred at 45°C for 2 hours. 2,6-Dichlorobenzothiazole (1.02 g, 5.00 mmol, 1.00 eq.) was added and stirring continued at 80°C for 20 hours. After cooling, the reaction mixture was poured onto 30 mL ice-cooled 0.5 N HCl, extracted with EtOAc, and the separated organic phase washed twice with brine, dried over Na_2SO_4, and the solvent evaporated in vacuo. The residue was recrystallized from Et_2O:hexane to provide 1.46 g (72%) light tan crystals: mp 170.5-2.5°C.
^1H NMR ($CDCl_3$) δ 4.07 (br d, J=6 Hz, 1H), 5.24 (br d, J=6 Hz, 1H), 7.16-7.58 (m, 14H); MS 405 (M^+); titration pK_a 6.6.

Analysis for $C_{22}H_{16}ClN_3OS$:
Calc.: C, 65.10; H, 3.97; N, 10.35;
Found: C, 64.85; H, 4.13; N, 10.12.

Example 10

1-[(4-Aminophenyl)aminocarbonyl]-4,5-diphenyl-3-pyrazolidinone

1-[(4-Nitrophenyl)aminocarbonyl]-4,5-diphenyl-3-pyrazolidinone (500 mg, 1.24 mmol) was dissolved in 50 mL EtOH and hydrogenated with 5% Pd/C (500 mg) under 60 p.s.i. H_2, overnight at room temperature. The mixture was filtered to remove catalyst, solvent removed in vacuo, and the product isolated by chromatography (0-50% EtOAc:hexane gradient) as 125 mg (27%) solid.
^1H NMR ($CDCl_3$) δ 3.97 (d, J=6 Hz, 1H), 5.50 (d, J=6 Hz, 1H), 6.58 (d, J=10 Hz, 2H), 6.96 (d, J=10 Hz, 2H), 7.2-7.5 (m, 10H); MS 372 (M^+); titration pK_a 4.5, 8.1.

Analysis for $C_{22}H_{20}N_4O_2$:
Calc.: C, 70.95; H, 5.41; N, 15.04;

Found: C, 70.65; H, 5.42; N, 14.75.

Example 11

1-[(4-Bromophenyl)aminocarbonyl]-2-(O-t-butyl-carboxymethyl)-4,5-diphenyl-3-pyrazolidinone and 1-[(4-bromophenyl)aminocarbonyl]-3-(O-t-butylcarboxymethoxy)-4,5-diphenyl-2-pyrazoline

To a suspension of 1-[(4-bromophenyl)amino-carbonyl]-4,5-diphenyl-3-pyrazolidinone (2.0 g, 4.6 mmol) in 30 mL abs. EtOH were added a solution of KOH (1.1 eq.) in abs. EtOH and t-butyl bromoacetate (5 mL).

After stirring for 3 days a precipitate of KBr had appeared. The mixture was diluted with H_2O, extracted with Et_2O, then the Et_2O layer washed with H_2O and brine, dried over Na_2SO_4, and evaporated in vacuo. An inseparable mixture of two products was isolated by chromatography (O-25% EtOAc:hexane gradient) as 1.3 g (52%) foam, containing a 3:2 ratio of N-alkylated to O-alkylated products [first and second title products, respectively] by NMR:

^{1}H NMR ($CDCl_3$) N-alkylated: δ 1.53 (s, 9H), 3.96 (d, J=19 Hz, 1H), 4.06 (s, 1H), 4.65 (d, J=19 Bz, 1H), 5.95 (s, 1H), 7.23-7.46 (m, 14H), 9.70 (s, 1H); O-alkylated: δ 1.53 (s, 9H), 4.18 (d, J=7 Hz, 1H), 4.67 (s, 2H), 5.40 (d, J=7 Hz, 1H), 7.23-7.46 (m, 14H), 7.74 (s, 1H); MS 549, 551 (M^+'s for Br isotopes).

Analysis for $C_{28}H_{28}BrN_3O_4$:

Calc.: C, 61.10; H, 5.13; N, 7.63;

Found: C, 60.94, H, 4.93; N, 7.85.

Example 12

1-[(4-Bromophenyl)aminocarbonyl]-2-carboxy-methyl-4,5-diphenyl-3-pyrazolidinone and 1-[(4-bromophenyl)aminocarbonyl]-3-carboxymethoxy-4,5-diphenyl-2-pyrazoline

The regioisomeric mixture of t-butyl esters from Example 11 [c. 3:2 mixture of N- to O-alkylated] (500 mg, 0.91 mmol) was dissolved in 30 mL CH_2Cl_2 and 5 mL trifluoroacetic acid. After 4 hours TLC (CH_2Cl_2) indicated disappearance of starting materials. Solvent was removed in vacuo and a mixture of two products isolated by chromatography (0-100% EtOAc:hexane gradient) as 180 mg (40%) foam, comprised of a 4:3 ratio of N-alkylated to O-alkylated compounds [first and second title products, respectively] by NMR.

^{1}H NMR ($CDCl_3$) N-alkylated: δ 4.09 (d, J=2 Hz, 1H), 4.10 (d, J=19 Hz, 1H), 4.68 (d, J=19 Hz, 1H), 5.83 (d, J=2 Hz, 1H), 7.20-7.50 (m, 14H), 9.08 (s, 1H); O-alkylated: δ 4.19 (d, J=5 Hz, 1H), 4.83 (ABq, J=16 Hz, Δu=30 Hz, 2H), 5.46 (d, J=5 Hz, 1H), 7.20-7.50 (m, 14H), 7.75 (s, 1H); MS 493, 495 (M^+s for Br isotopes); titration pK_a 4.8.

Analysis for $C_{24}H_{20}BrN_3O_4$:

Calc.: C, 58.31; H, 4.08; N, 8.50;

Found: C, 58.59; H, 4.03; N, 8.24.

The N- and O-alkylated products were separated by chromatography on a Waters C_{18} reverse-phase column, using 30-40% CH_3CN:H_2O buffered with 0.3-0.5% NH_4OAc. The leading fractions from the first pass were evaporated, lyophilized, then taken up in CH_2Cl_2, washed twice with 1 N HCl, and the solvent removed in vacuo to provide 28 mg O-alkylated product:

^{1} H NMR ($CDCl_3$ δ 4.19 (d, J=7 Hz, 1H), 4.84 (ABq, J=17 Hz, Δu=25 Hz, 2H), 5.45 (d, J=7 Hz, 1H), 6.39 (br s, 1H), 7.20-7.40 (m, 14H), 7.70 (s, 1H).

The later fractions were rechromatographed twice more, then similarly processed to give 8 mg N-alkylated product:

^{1}H NMR ($CDCl_3$) δ $CDCl_3$ 4.05 (s, 1H), 4.08 (br d, J=18 Hz, 1H), 4.70 (br d, J=18 Hz, 1H), 5.82 (s, 1H), 7.21-7.50 (m, 14H), 9.0 (br s, 1H).

Example 13

1-[(4-Trifluoromethylphenyl)aminocarbonyl]-3-methoxy-4,5-diphenyl-2-pyrazoline

A solution of 1-[(4-trifluoromethylphenyl)-aminocarbonyl]-4,5-diphenyl-3-pyrazolidinone (740 mg, 1.74 mmol) and KOH (122 mg of 88% pure, 1.1 eq.) in 30 mL abs. EtOH was treated with iodomethane (5 mL) and stirred overnight. The mixture was diluted with H_2O, extracted twice with CH_2Cl_2, and the combined extracts washed with H_2O, dried over Na_2SO_4, and evaporated in vacuo. The product was isolated by chromatography (0-15% EtOAc:hexane gradient) as 61 mg (8%) solid.

^{1}H NMR ($CDCl_3$) δ 4.0 (s, 3H), 4.11 (d, J=6 Hz, 1H), 5.48 (d, J=6 Hz, 1H), 7.2-7.74 (m, 14H), 8.09 (s, 1H); MS 439 (M^+).

Also isolated was 1-[(4-trifluoromethylphenyl)-aminocarbonyl]-2-methyl-4,5-diphenyl-3-pyrazolidinone, corresponding to a product prepared, according to the method of Example 1, from 2-methyl-4,5-diphenyl-3-pyrazolidinone and 4-trifluoromethylphenylisocyanate.

Example 14

1-(Indole-2-carbonyl)-4,5-diphenyl-3-pyrazolidinone

Indole-2-carboxylic acid (1.35 g, 8.38 mmol), oxalyl chloride (4 mL), and DMF (3 drops) were added in order to 50 mL toluene, and stirred until gas evolution subsided and a homogeneous solution was obtained (c.20 min). Solvent was removed in vacuo, the residue taken up in CH_2Cl_2, and added to a solution of 4,5-diphenyl-3-pyrazolidinone (2.0 g, 8.40 mmol, 1.00 eq.) in 50 mL CH_2Cl_2 and 5 mL pyridine. After stirring overnight, the solution was washed with 1N HCl, dried over Na_2SO_2, and solvent removed in vacuo. The residual solid was stirred with CH_2Cl_2, filtered, and recrystallized from DMF:H_2O to give 1.42 g (44%) white solid: mp 248-50°C. ^{1}H NMR (d_6-DMSO) δ 3.82 (s, 1H), 5.86 (s, 1H), 6.95-7.6 (m, 16H), 11.84 (br s, 1H); MS 381 (M^+); titration pK_a 6.75.

Analysis for $C_{24}H_{19}N_3O_2$:

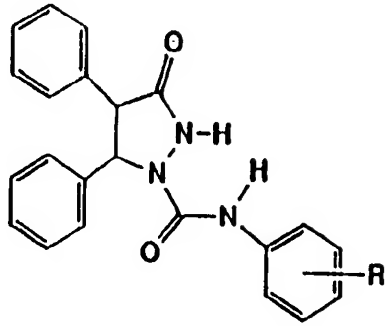
Calc.: C, 75.57; H, 5.02; N, 11.02;

Found: C, 75.38, H, 5.21; N, 10.99

Examples 15-135 are summarized below in Table 1. The compound of each Example is identified by reference to the structural formula preceeding each group of Examples. The method for preparing each compound is indicated by reference to the Methods A-O, corresponding to the procedures identified in the foregoing Examples 1-9. The phenyl groups on the pyrazolidinone ring of the compounds of Examples 1-67 and 74-109 are in the trans position.

TABLE I

PHYSICAL CHEMISTRY DATA ON CCK / GASTRIN ANTAGONISTS



Structure for examples 15-59 below

Ex.	R	Method of Prep.	Solvent of Cryst.[a]	Yield, %	Mp. °C	MS	1HNMR	Formula	Analysis, % Theory/Found C	H	N
15	H	A	EtOAc: hexane	2.20 g 73%	168-70	357 (M+)	DMSO 3.75 (s, 1H), 5.58 (s, 1H), 6.96-7.53 (m, 15H), 9.16 (s, 1H), 10.8 (s, 1H)	C22H19N3O2	73.93 73.84	5.36 5.42	11.76 11.75
16	4-CF3	A (THF)	PhMe	2.32 g 43.3%		426 (M+1)	DMSO 3.80 (br s, 1H), 5.58 (br s, 1H), 7.30-7.80 (m, 14H), 9.54 (br s, 1H), 10.90 (br s, 1H)	C23H18F3N3O2	64.94 64.67	4.26 4.09	9.88 9.75
17	4-F	A	EtOAc: hexane	1.76 g 65%	189-91	375 (M+)	CDCl3 3.99 (d, J=6 Hz, 1H), 5.53 (d, J=6 Hz, 1H), 6.85-7.5 (m, 14 H), 8.95 (br s, 1H)	C22H18FN3O2	70.37 70.24	4.83 4.85	11.17 11.09
18	4-Cl	A	EtOAc: hexane	2.44 g 48%	173-5	391 (M+)	DMSO 3.78 (s, 1H), 5.56 (s, 1H), 7.24-7.6 (m, 14H), 9.32 (s, 1H), 10.81 (s, 1H)	C22H18ClN3O2	67.43 67.30	4.63 4.79	10.72 10.67
19	4-Cl (N-Me)	B	chrom (prep plates)	60 mg 40%		405 (M+)	CDCl3 3.18 (s, 3H), 3.53 (d, J=3 Hz, 1H), 4.86 (d, J=3 Hz, 1H), 6.9-7.42 (m, 15H)	C23H20ClN3O2			

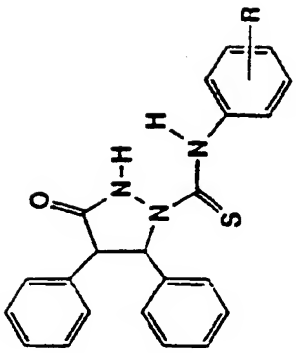
Ex.	R	Method of Prep.	Solvent of Crystl.[a]	Yield, %	Mp. °C	MS	1HNMR	Formula	Analysis, % Theory/Found C	H	N
20	4-Br	A (THF)	PhMe (to give PhMe hemi-solvate)	2.64 g 58%	174-6[b]	435, 437 (M+'s for Br isotopes)	DMSO 3.77 (br s, 1H), 5.57 (br s, 1H), 7.12-7.55 (m, 14H), 9.31 (br s, 1H), 10.81 (br s, 1H)	C22H18BrN3O2· 1/2 (C7H8)	63.49 63.15	4.60 4.60	8.71 8.81
21	4-I	C	EtOAc: hexane	90 mg 2%	177-9	483 (M+)	CDCl3 4.0 (d, J=6 Hz, 1H) , 5.54 (d, J=6 Hz, 1H), 6.9-7.5 (m, 14H)	C22H18IN3O2	54.67 54.46	3.75 3.70	8.69 8.51
22	4-CO2Et	A	chrom	480 mg 11%		430 (M+1)	CDCl3 1.38 (t, J=8 Hz, 3H), 4.02 (d, J=6 Hz, 1H), 4.34 (q, J=8 Hz, 2H), 5.56 (d, J=6 Hz, 1H), 7.18-7.95 (m, 14H)	C25H23N3O4			
23	4-COMe	A	chrom	31 mg 1.2%		399 (M+)	CDCl3 2.52 (s, 3H), 4.03 (d, J=6 Hz, 1H), 5.55 (d, J=6 Hz, 1H), 7.31 (d, J=12 Hz, 2H), 7.2-7.5 (m, 11 Hz), 7.83 (d, J=12 Hz, 2H), 9.18 (br s, 1H)	C24H21N3O3			
24	4-NO2	A	EtOAc: hexane	1.8 g 71%	168-70	402 (M+)	DMSO 3.83 (s, 1H), 5.58 (s, 1H), 7.25-7.5 (m, 10H), 7.82 (d, J=14 Hz, 2H), 8.2 (d, J=14 Hz, 2H), 9.77 (s, 1H), 11.03 (br s, 1H)	C22H18N4O4	65.67 65.43	4.51 4.56	13.92 13.70
25	4-Me	A	PhMe	1.72 g 44%		371 (M+)	DMSO 2.25 (s, 3H), 3.75 (s, 1H), 5.57 (br s, 1H), 7.08 (d, J=8 Hz, 2H), 7.3-7.5 (m, 12H), 9.03 (br s, 1H), 10.74 (br s, 1H)	C23H21N3O2	74.37 74.52	5.70 5.50	11.31 11.10
26	4-Et	A	triturated with PhMe	3.74 g 92%		385 (M+)	DMSO 1.16 (t, J=8 Hz, 3H), 2.55 (q, J=8 Hz, 2H), 3.74 (br s, 1H), 5.57 (br s, 1H), 7.12 (d, J=9 Hz, 2H), 7.14- 7.54 (m, 12H), 9.06 (br s, 1H), 10.76 (br s, 1H)	C24H23N3O2	74.78 75.00	6.01 6.13	10.90 10.71
27	4-n-Pr	C	EtOAc: hexane	230 mg 6%	169-71	400 (M+1)	CDCl3 0.9 (t, J=10 Hz, 3H), 1.58 (m, 2H), 2.5 (t, J=10 Hz, 2H), 4.0 (d, J=6 Hz, 1H), 5.54 (d, J=6 Hz, 1H), 6.82 (s, 1H), 7.03 (d, J=12 Hz, 2H), 7.1 (d, J=12 Hz, 2H), 7.23 7.5 (m, 10H), 8.62 (br s, 1H)	C25H25N3O2	75.16 75.07	6.31 6.23	10.52 10.50

Ex.	R	Method of Prep.	Solvent of Cryst.[a]	Yield, %	Mp. °C	MS	1HNMR	Formula	Analysis, % Theory/Found C	H	N
28	4-n-Bu	A	EtOAc: hexane	1.22 g 47%	165-7	413 (M+)	CDCl3 0.95 (t, J=10 Hz, 3H), 1.3 (m, 2H), 1.5 (m, 2H), 2.56 (t, J=10 Hz, 2H), 3.98 (d, J=6 Hz, 1H), 5.54 (d, J=6 Hz, 1H), 6.93 (s, 1H), 7.03 (d, J=12 Hz, 2H), 7.1 (d, J=12 Hz, 2H), 7.23-7.46 (m, 10H), 9.04 (s, 1H)	C26H27N3O2	75.52 75.23	6.58 6.35	10.16 9.97
29	4-i-Pr	A	THF: EtOAc	1.0 g 40%	191-3	399 (M+)	CDCl3 1.21 (d, J=10 Hz, 6H), 2.83 (m, J=10 Hz, 1H), 4.0 (d, J=6 Hz, 1H), 5.53 (d, J=6 Hz, 1H), 6.83 (s, 1H), 7.1-7.5 (m, 14H), 8.65 (s, 1H)	C25H25N3O2	75.16 75.37	6.31 6.42	10.52 10.46
30	4-t-Bu	C	EtOAc	790 mg 30%	204-7	413 (M+)	CDCl3 1.26 (s, 9H), 4.0 (d, J=6 Hz, 1H), 5.50 (d, J=6 Hz, 1H), 6.83 (s, 1H), 7.12 (d, J=12 Hz, 2H), 7.35 (d, J=12 Hz, 2H), 7.2-7.44 (m, 10H), 8.6 (s, 1H)	C26H27N3O2	75.52 75.74	6.58 6.78	10.16 10.18
31	4-c-Hexyl	B	chrom, then EtOAc, then chrom	104 mg 3%	200-3	439 (M+)	DMSO 1.15-1.85 (m, 10H), 2.22 (m, 1H), 3.74 (s, 1H), 5.58 (s, 1H), 7.13 (d, J=12 Hz, 1H), 7.46 (d, J=12 Hz, 1H), 7.3-7.43 (m,10H), 9.08 (s, 1H), 10.76 (s, 1H)	C28H29N3O2	76.51 76.29	6.65 6.81	9.56 9.38
32	4-Ph	C	chrom, then, EtOAc: hexane	312 mg 17%	180-2	433 (M+)	CDCl3 4.02 (d, J=6 Hz, 1H), 5.60 (d, J=6 Hz, 1H), 7.2-7.56 (m, 20H), 9.4 (br s, 1H)	C28H23N3O2	76.94 76.86	5.50 5.39	9.97 9.96
33	4-OMe	A	EtOAc: hexane	1.9 g 79%	154-7	387 (M+)	CDCl3 3.74 (s, 3H), 3.96 (d, J=6 Hz, 1H), 5.53 (d, J=6 Hz, 1H), 6.74 (d, J=12 Hz, 2H), 7.15 (d, J=12 Hz, 2H), 6.9-7.43 (m, 11H), 9.0 (br s, 1H)	C23H21N3O3	71.30 70.71	5.46 5.67	10.85 10.71
34	4-OEt	A	triturated with PhMe	2.93 g 87%		401 (M+)	DMSO 1.31 (t, J=7 Hz, 3H), 3.73 (s, 1H), 3.97 (q, J=7 Hz, 2H), 5.55 (br s, 1H), 6.84 (d, J=8 Hz, 2H), 7.3-7.53 (m, 12H), 8.99 (br s, 1H), 10.72 (br s, 1H)	C24H23N3O3	71.80 72.05	5.77 5.89	10.47 10.21

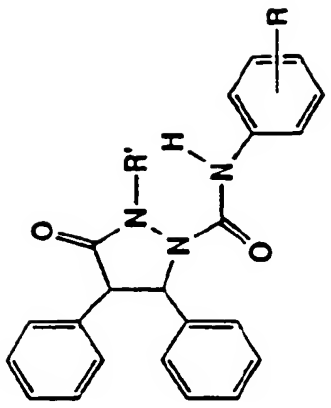
Ex.	R	Method of Prep.	Solvent of Cryst.[a]	Yield, %	Mp. °C	MS	1HNMR	Formula	Analysis, % Theory/Found C	H	N
35	4-O-i-Pr	B	triturated with Et2O	1.34 g 74%	178-80	415 (M+)	CDCl3 1.27 (d, J=8 Hz, 6H), 3.93 (d, J=5 Hz, 1H), 4.42 (septet, J=6 Hz, 1H), 5.54 (d, J=5 Hz, 1H), 6.72 (d, J=9 Hz, 2H), 6.95 (s, 1H), 7.05 (d, J=9 Hz, 2H), 7.13-7.39 (m, 11H)	C25H25N3O3	72.27 72.25	6.06 6.04	10.11 10.06
36	4-OCH2CH2Ph	B	chrom (EtOAc: hexane), then triturated with PhMe	324 mg 31%		477 (M+)	DMSO 3.01 (t, J=7 Hz, 2H), 3.73 (s, 1H), 4.14 (t, J=7 Hz, 2H), 5.55 (br s, 1H), 6.86 (d, J=9 Hz, 2H), 7.18-7.52 (m, 17H), 9.01 (br s, 1H), 10.72 (br s, 1H)	C30H27N3O3	75.45 75.71	5.70 5.78	8.80 8.67
37	4-OPh	A	EtOAc: CH3OH	2.9 g 68%	188-90	450 (M+1)	DMSO 3.75 (s, 1H), 5.59 (s, 1H), 6.95-7.56 (m, 19H), 9.21 (s, 1H), 10.8 (s, 1H)	C28H23N3O3	74.82 74.58	5.16 5.22	9.35 9.34
38	4-SMe	A	EtOAc: hexane	1.6 g 65%	160-2	403 (M+)	CDCl3 2.42 (s, 3H), 4.0 (d, J=6 Hz, 1H), 5.54 (d, J=6 Hz, 1H), 6.95-7.44 (m, 15H), 8.98 (br s, 1H)	C23H21N3O2S	68.46 68.28	5.25 5.28	10.41 10.25
39	3-CF3	A	EtOAc: hexane	3.0 g 83%	165-7	425 (M+)	DMSO 3.8 (s, 1H), 5.58 (s, 1H), 7.3-7.56 (m, 12H), 7.82 (d, 1H), 7.98 (s, 1H), 9.54 (s, 1H), 10.88 (s, 1H)	C23H18F3N3O2	64.94 65.07	4.27 4.19	9.88 9.77
40	3-NO2	A	EtOAc: hexane	2.11 g 84%	164-6	(no M+)	CDCl3 4.03 (d, J=6 Hz, 1H), 5.62 (d, J=6 Hz, 1H), 7.2-8.1 (m, 14H)	C22H18N4O4	65.57 65.53	4.51 4.25	13.92 13.67
41	3-Me	A	CH3OH	1.05 g 46%	188-90	371 (M+)	DMSO 3.3 (s, 3H), 3.74 (s, 1H), 5.57 (s, 1H), 6.8-7.54 (m, 12H), 9.04 (s, 1H), 10.86 (s, 1H)	C23H21N3O2	74.37 74.17	5.70 5.63	11.31 11.04
42	3-OMe	A	EtOAc: hexane	2.1 g 51%	163-5	387 (M+)	CDCl3 3.7 (s, 3H), 3.98 (d, J=6 Hz, 1H), 5.54 (d, J=6 Hz, 1H), 6.56-7.48 (m, 16H)	C23H21N3O3	71.30 71.29	5.46 5.72	10.85 10.59
43	3-O-i-Pr	B	C6H6: hexane	450 mg 22%	80-85	415 (M+)	CDCl3 1.26 (d, J=6 Hz, 6H), 3.96 (d, J=5 Hz, 1H), 4.45 (septet, J=6 Hz, 1H), 5.51 (d, J=5 Hz, 1H), 6.54-6.62 (m, 2H), 6.91-7.08 (m, 3H), 7.21-7.50 (m, 11H)	C25H25N3O3	72.27 71.99	6.06 6.18	10.11 9.94

Ex.	R	Method of Prep.	Solvent of Crysl.[a]	Yield, %	Mp. °C	MS	1HNMR	Formula	Analysis, % Theory/Found C	H	N
44	3 OCH2Ph	B	triturated with Et2O	1.64 g 85%	143-44.5	463 (M+)	CDCl3 3.99 (d, J=5 Hz, 1H), 4.97 (s, 2H), 5.54 (d, J=5 Hz, 1H), 6.66-6.68 (m, 2H), 7.06 (s, 1H), 7.09-7.12 (m, 2H), 7.23-7.44 (m, 16H)	C29H25N3O3	75.14 75.01	5.44 5.49	9.07 8.84
45	3-CF3,4-Br	B	chrom	120 mg 12%		503, 505 (M+'s for Br isotopes)	CDCl3 4.03 (d, J=6 Hz, 1H), 5.58 (d, J=6 Hz, 1H), 7.2-7.56 (m, 15H)	C23H17BrF3N3O2	54.78 55.05	3.40 3.51	8.33 8.07
46	3,4-diCl	A	EtOAc: hexane	2.2 g 49%	169-71	425 (M+)	CDCl3 4.04 (d, J=6 Hz, 1H), 5.57 (d, J=6 Hz, 1H), 6.97-7.5 (m, 15H)	C22H17Cl2N3O2	61.99 62.22	4.02 4.11	9.86 9.75
47	3-Cl,4-F	A	EtOAc: hexane	2.0 g 84%	174-6	409 (M+)	CDCl3 4.0 (d, J=6 Hz, 1H), 5.56 (d, J=6 Hz, 1H), 6.95-7.5 (m, 15H)	C22H17ClFN3O2	64.47 64.03	4.18 4.76	10.25 9.53
48	3-NO2,4-Cl	A	EtOAc: hexane	910 mg 41%	149-51	436 (M+)	CDCl3 4.03 (d, J=6 Hz, 1H), 5.58 (d, J=6 Hz, 1H), 7.2-7.82 (m, 14H), 9.3 (s,1H)	C22H17ClN4O4	60.49 60.23	3.92 4.03	12.83 12.79
49	3,4-(CH2)3	B	EtOAc: hexane, then chrom (EtOAc: hexane), then EtOAc	380 mg 12%	179-81	397 (M+)	DMSO 1.97 (m, 2H), 2.8 (m, 4H), 3.7 (s, 1H), 5.58 (s, 1H), 7.12-7.5 (m, 13H), 9.0 (s, 1H), 10.75 (s, 1H)	C25H23N3O2	75.55 75.67	5.83 5.95	10.57 10.46
50	3,4-(CH2)4	D	chrom (EtOAc: CH2Cl2), then Et2O: CH2Cl2	354 mg 20%	177-8.5	411 (M+)	CDCl3 1.74 (t, J=3 Hz, 4H), 2.66 (d, J=7 Hz, 4H), 3.97 (d, J=5 Hz, 1H), 5.55 (d, J=5 Hz, 1H), 6.83-6.92 (m, 3H), 6.98 (s, 1H), 7.24-7.44 (m, 10H), 9.06 (br s, 1H)	C26H25N3O2	75.89 76.08	6.12 6.33	10.21 10.05
51	3,4-diOMe	B	chrom	640 mg 11%		418 (M+1)	CDCl3 3.74 (s, 3H), 3.82 (s, 3H), 3.97 (d, J=6 Hz, 1H), 5.58 (d, J=6 Hz, 1H), 6.53-7.5 (m, 14H), 8.7 (s, 1H)	C24H23N3O4	69.05 68.92	5.55 5.54	10.07 10.12

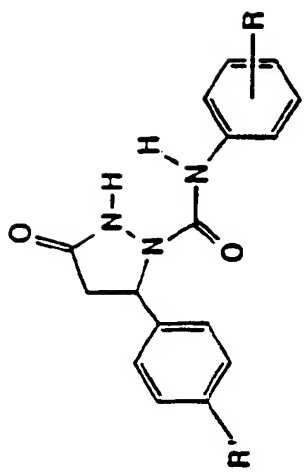
Ex.	R	Method of Prep.	Solvent of Cryst.[a]	Yield, %	Mp. °C	MS	1HNMR	Formula	Analysis, % Theory/Found C	H	N
52	3,4-OCH2O	B	EtOAc	390 mg 7%	179-81	401 (M+)	DMSO 3.73 (s, 1H), 5.55 (s, 1H), 5.97 (s, 2H), 6.8-7.6 (m, 13 H), 9.05 (s, 1H), 10.75 (s, 1H)	C23H19N3O4	68.82 68.98	4.77 4.76	10.47 10.29
53	2-CF3	A	EtOAc	3.46 g 77%	143-5	425 (M+)	DMSO 3.8 (s, 1H), 5.6 (s, 1H), 7.2-7.75 (m, 14H), 8.68 (s, 1H), 10.95 (s, 1H)	C23H16F3N3O2	64.94 65.15	4.26 4.19	9.88 9.60
54	2,3-diCl	A	THF: hexane	3.9 g 70%	191-3	425 (M+)	DMSO 3.78 (s, 1H), 5.54 (s, 1H), 7.3-7.6 (m, 13H), 8.88 (s, 1H), 11.05 (s, 1H)	C22H17Cl2N3O2	61.93 62.00	4.02 3.96	9.86 9.94
55	2,4-diCl	A	EtOAc: hexane	1.7 g 63%	150-3	425 (M+)	CDCl3 4.02 (d, J=6 Hz, 1H), 5.38 (d, J=6 Hz, 1H), 7.15-7.5 (m, 13H), 8.1 (d, J=10 Hz, 1H), 8.95 (s, 1H)	C22H17Cl2N3O2	61.98 62.16	4.02 4.28	9.86 9.98
56	2,4-diF	A	chrom	800 mg 32%		393 (M+)	CDCl3 4.03 (d, J=6 Hz, 1H), 5.43 (d, J=6 Hz, 1H), 6.8 (m, 2H), 6.91 (s, 1H), 7.2-7.5 (m, 9H), 7.93 (m, 1H), 8.8 (br s, 1H)	C22H17F2N3O2			
57	2-Cl,5-CF3	A	EtOAc: hexane	1.38 g 29%	130-2	459 (M+)	CDCl3 4.05 (d, J=6 Hz, 1H), 5.41 (d, J=6 Hz, 1H), 7.2-7.5 (m, 14H), 8.53 (s, 1H)	C23H17ClF3N3O2	60.07 60.37	3.73 3.95	9.14 9.03
58	3,5-diCF3	A	chrom	3.6 g 69%		493 (M+)	CDCl3 4.03 (d, J=6 Hz, 1H), 5.62 (d, J=6 Hz, 1H), 7.2-7.58 (m, 13H), 7.75 (s, 2H)	C24H17F6N3O2	58.42 58.59	3.47 3.75	8.52 8.69
59	3,5-diCl	A	EtOAc: hexane	800 mg 30%	166-8	425 (M+)	DMSO 3.82 (s, 1H), 5.54 (s, 1H), 7.2 (s, 1H), 7.15-7.5 (m, 10H), 7.71 (s, 2H), 9.5 (s, 1H), 10.95 (s, 1H)	C22H17Cl2N3O2	61.99 61.75	4.02 3.94	9.86 9.65



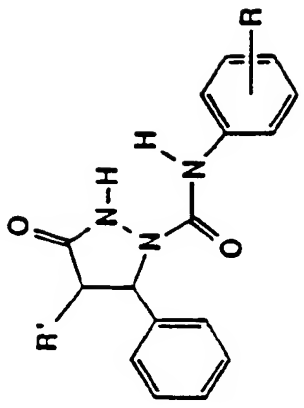
Ex.	R	Method of Prep.	Solvent of Crystl.[a]	Yield, %	Mp. °C	MS	^{1}HNMR	Formula	Analysis, % Theory/Found C	H	N
60	H	A (Title)	PhMe:hexane, then Et2O: hexane (to give Et2O solvate)	117 mg 5%	69-79	373 (M+)	CDCl3 4.03 (d, 1H), 5.77 (d, 1H), 7.10-7.54 (m, 18 H), 9.6 (br s, 1H) [plus for Et2O: 1.20 (t, 6H), 3.48 (q, 4H)]	C22H19N3OS-C4H10O	69.77 69.72	6.53 6.38	9.39 9.37
61	3-CF3	A	chrom	1.5 g 33%		442 (M+1)	CDCl3 4.07 (d, J=6 Hz, 1H), 5.82 (d, J=6 Hz, 1H), 7.12-7.63 (m, 16H)	C23H18F3N3OS	62.58 62.87	4.11 4.22	9.52 9.34
62	4-CF3	A	PhMe	800 mg 29%	87-90	441 (M+), 442 (M+1)	CDCl3 4.09 (d, J=6 Hz, 1H), 5.77 (d, J=6 Hz, 1H), 7.16 (d, J=9 Hz, 1H), 7.2-7.28 (m, 3H), 7.3-7.44 (m, 7H), 7.44 7.64 (m, 5H)	C23H18F3N3OS	62.51 62.51	4.11 4.15	9.52 9.46
63	3-CF3,4-Cl	A	chrom, then triturated with hexane	200 mg 10%	80-2	475 (M+), 476 (M+1)	CDCl3 4.09 (d, J=6 Hz, 1H), 5.83 (d, J=6 Hz, 1H), 7.06-7.6 (m, 15H)	C23H17ClF3N3OS	58.05 58.15	8.82 8.55	3.60 3.82
64	2,3-diCl	A	EtOAc: hexane	2.5 g 67%	154-6	441 (M+), 442, 444 (M+1's for Cl isotopes)	DMSO 3.85 (s, 1H), 6.16 (s, 1H), 7.2-7.6 (m, 13H), 9.5 (br s, 1H), 11.5 (br s, 1H)	C22H17Cl2N3OS	59.73 59.92	3.87 4.11	9.50 9.73
65	pentaF	A	chrom	600 mg 21%		463 (M+)	CDCl3 4.04 (d, J=5 Hz, 1H), 5.82 (s, 1H), 6.94 (s, 1H), 7.2-7.55 (m, 11H)	C22H14F5N3OS			



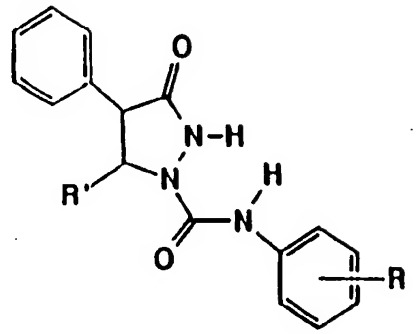
Ex.	R	R'	Method of Prep.	Solvent of Cryst.[a]	Yield, %	Mp.°C	MS	^{1}HNMR	Formula	Analysis, % Theory/Found C	H	N
66	2,3-diCl	Me	A	EtOAc: hexane	670 mg 76%	172-4	439 (M+)	DMSO 3.35 (s, 3H), 3.88 (s, 1H), 5.50 (s, 1H), 7.16-7.56 (m, 13H), 9.26 (s, 1H)	C23H19Cl2N3O2	62.74 62.55	4.35 4.26	9.54 9.37
67	4-CF3	Me	A	chrom	210 mg 40%		439 (M+)	CDCl3 3.36 (s, 3H), 3.93 (d, J=3 Hz, 1H), 5.54 (d, J=3 Hz, 1H), 6.92 (s, 1H), 7.15-7.6 (m, 14H)	C24H20F3N3O2	65.60 65.35	4.59 4.51	9.56 9.30



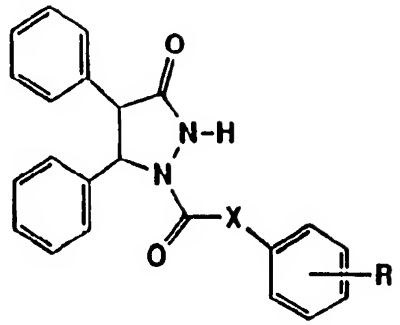
Ex.	R	R'	Method of Prep.	Solvent of Cryst.[a]	Yield, %	Mp °C	MS	1HNMR	Formula	Analysis, % Theory/Found C	H	N
68	2,3-diCl	Ph	A	EtOAc	170 mg 63%	172-3	425 (M+)	DMSO 2.5 (m, 1H), 3.53 (m, 1H), 5.72 (s, 1H), 7.3-7.78 (m, 11H), 7.95 (s, 1H), 8.58 (s, 1H), 10.6 (br s, 1H)	$C_{22}H_{17}Cl_2N_3O_2$	61.96 62.20	4.02 4.04	9.86 9.94



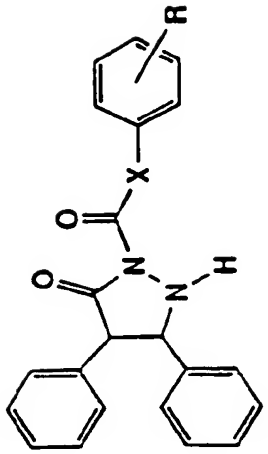
Ex.	R	R'	Method of Prep.	Solvent of Cryst.[a]	Yield, %	Mp °C	MS	1HNMR	Formula	Analysis, % Theory/Found C	H	N
69	4-Br	n-Bu	A	chrom	670 mg 56%		415, 417 (M+'s for Br isotopes)	DMSO 0.84 (t, J=12 Hz, 3H), 1.30 (m, 2H), 1.46 (m, 2H), 1.65 (m, 2H), 3.29 (s, 1H), 5.38 (s, 1H), 7.2-7.6 (m, 9H), 9.17 (s, 1H), 10.34 (s, 1H)	$C_{20}H_{22}BrN_3O_2$			



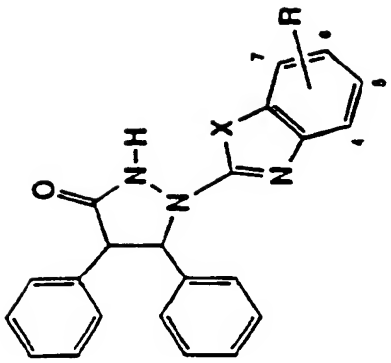
Ex.	R	R'	Method of Prep.	Solvent of Cryst.[a]	Yield, %	Mp. °C	MS	1H NMR	Formula	Analysis, % Theory/Found C	H	N
70	3-CF3	n-Bu	A	chrom	290 mg 21%		405 (M+)	CDCl3 0.93 (t, J=12 Hz, 3H), 1.42 (m, 2H), 1.5 (m, 2H), 1.73 (m, 1H), 1.83 (m, 1H), 3.79 (s, 1H), 4.83 (m, 1H), 7.2-7.6 (m, 9H), 7.74 (s, 1H), 7.83 (s, 1H)	C21H22F3N3O2	62.21 62.40	5.47 5.66	10.36 10.26
71	4-CF3	n-Bu	A	chrom	136 mg 15%	152-5	405 (M+)	CDCl3 0.95 (t, J=8 Hz, 3H), 1.42 (m, 2H), 1.51 (m, 2H), 1.72 (m, 1H), 1.88 (m, 1H), 3.53 (s, 1H), 4.82 (t, J=8 Hz, 1H), 7.18-7.35 (m, 5H), 7.44 (ABq, J=8 Hz, Δν=18 Hz, 4H), 7.65 (s, 1H), 8.55 (v br s, 1H)	C21H22F3N3O2	62.21 61.97	5.47 5.56	10.36 10.22
72	4-Br	CH2Ph	A	EtOAc: hexane	248 mg 51%		449, 451 (M+'s for Br isotopes)	DMSO 2.97-3.15 (m, 2H), 3.47 (br s, 1H), 4.70 (br s, 1H), 7.01 (d, J=8 Hz, 2H), 7.15-7.42 (m, 12H), 9.05 (br s, 1H), 10.47 (br s, 1H)	C23H20BrN3O2	61.34 61.16	4.48 4.73	9.33 9.12
73	4-Br	i-Pr	A	chrom (EtOAc: hexane)	45 mg 42%		401, 403, (M+'s for Br isotopes)	CDCl3 1.12 (d, J=6 Hz, 6H), 2.05 (m, J=7 Hz, 1H), 3.64 (s, 1H), 4.56 (d, J=8 Hz, 1H), 7.20-7.51 (m, 9H), 8.28 (br s, 1H)	C19H20BrN3O2			



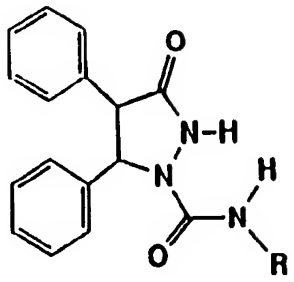
Ex.	R	X	Method of Prep.	Solvent of Cryst.[a]	Yield, %	Mp. °C	MS	1HNMR	Formula	Analysis, % Theory/Found C	H	N
74	4-CF3	-	E (Et3N)	c	100 mg 6%	72-5	410 (M+)	CDCl3 3.89 (d, J=4 Hz, 1H), 5.16 (br s, 1H), 7.18-7.26 (m, 5H), 7.26-7.50 (m, 8H), 7.50-7.57 (m, 2H)	C23H17F3N2O2	67.31 67.57	4.18 4.45	6.83 6.64
75	3,4-diCl	-	E (no base)	c	508 mg 29%	68-70	410, 412 (M+'s for Cl isotopes)	CDCl3 3.89 (d, J=4 Hz, 1H), 5.18 (br s, 1H), 7.14-7.48 (m, 14H)	C22H16Cl2N2O2	64.25 64.21	3.92 3.99	6.81 6.80
76	3-CF3	CH2	E	chrom	600 mg 17%		424 (M+)	CDCl3 3.47 (s, 2H), 3.94 (s, 1H), 5.30 (s, 1H), 7.0-7.8 (m, 14H)	C24H19F3N2O2	67.92 67.76	4.51 4.56	6.60 6.79
77	4-CF3	CH2	E (no base)	c	101 mg 6%	66-68	424 (M+)	CDCl3 3.48 (br s, 2H), 3.91 (d, J=4 Hz, 1H), 5.28 (br s, 1H), 7.04-7.5 (m, 15H)	C24H19F3N2O2	67.92 67.78	4.51 4.56	6.60 6.45
78	3,4-diCl	CH2	E (Et3N)	Et2O: hexane	1.0 g 17%	70-72	426 (M+)	CDCl3 3.36 (br s, 2H), 3.93 (d, J=5 Hz, 1H), 5.27 (br s, 1H), 6.84 (br s, 1H), 7.0 (br s, 1H), 7.08-7.5 (m, 12H)	C23H18Cl2N2O2	64.95 64.93	4.27 4.67	6.59 6.60
79	H	O	F	EtOAc: hexane	980 mg 43%	164-6	358 (M+)	CDCl3 3.97 (d, J=6 Hz, 1H), 5.54 (d, J=6 Hz, 1H), 6.9-7.5 (m, 16H)	C22H18N2O3	73.73 73.94	5.06 5.29	7.82 7.88
80	4-NO2	O	F	EtOAc	1.3 g 32%	175-7	403 (M+)	CDCl3 4.02 (d, J=6 Hz, 1H), 5.52 (d, J=6 Hz, 1H), 7.1-7.5 (m, 12H), 8.19 (d, J=15 Hz, 2H), 9.25 (br s, 1H)	C22H17N3O5	65.51 65.49	4.25 4.31	10.42 10.34
81	4-Br	S	B	EtOAc: hexane	610 mg 13%	156-7	452, 454 (M+'s for Br isotopes)	CDCl3 3.97 (d, J=4 Hz, 1H), 5.58 (d, J=4 Hz, 1H), 7.25-7.55 (m, 14H), 9.15 (br s, 1H)	C22H17BrN2O2S	58.29 58.04	3.78 3.79	6.18 6.07



Ex.	R	X	Method of Prep.	Solvent of Cryst.[a]	Yield, %	Mp. °C	MS	1HNMR	Formula	Analysis, % Theory/Found C	H	N
82	3-CF3	NH	N	chrom (CH2Cl2)	1.72 g 48%		425 (M+)	CDCl3 4.22 (d, J=12 Hz, 1H), 4.82 (dd, J=9 Hz, 12 Hz, 1H), 5.46 (d, J=9 Hz, 1H), 7.18-7.75 (m, 13H), 7.84 (s, 1H), 10.35 (s, 1H)	C23H18F3N3O2			
83	4-CF3	NH	N	chrom (CH2Cl2), then triturated with hexane	530 mg 30%	74-6	425 (M+)	CDCl3 4.23 (d, J=12 Hz, 1H), 4.82 dd, J=9, 12 Hz, 1H), 5.44 (d, J=9 Hz, 1H), 7.18-7.24 (m, 2H), 7.3-7.42 (m, 8H), 7.56-7.7 (m, 4H), 10.4 (br s, 1H)	C24H18F3N3O2	64.94 65.11	4.27 4.41	9.88 9.65



Ex.	R	X	Method of Prep.	Solvent of Cryst.[a]	Yield, %	Mp °C	MS	^{1}HNMR	Formula	Analysis, % Theory/Found C	H	N
84	H	S	O (C6H6)	Et2O	233 mg 42%	186-8	371 (M+)	CDCl3 4.05 (d, 1H), 5.23 (d, 1H), 7.15-7.68 (m, 15H)	C22H17N3OS	71.14 71.38	4.61 4.89	11.31 11.11
85	6-Br	S	O (PhMe)	Et2O: hexane	1.67 g 57%	180-6	449, 451 (M+'s for Br isotopes)	CDCl3 4.06 (d, J=7 Hz, 1H), 5.24 (d, J=7 Hz, 1H), 7.16-7.52 (m, 13H), 7.64 (d, J=1 Hz, 1H)	C22H16BrN3OS	58.67 58.87	3.58 3.83	9.33 9.08
86	4,5-diCl	S	O (PhMe)	Et2O: hexane	1.10 g 83%	200-4	440 (M+1 for Cl isotopes)	CDCl3 4.13 (d, J=8 Hz, 1H), 5.19 (d, J=8 Hz, 1H), 7.18-7.45 (m, 13H)	C22H15Cl2N3OS	60.01 60.30	3.43 3.70	9.54 9.62
87	H	O	O (PhMe)	Et2O	660 mg 62%	174-5.5	355 (M+)	CDCl3 4.04 (d, J=4.5 Hz, 1H), 5.60 (d, J=4.5 Hz, 1H), 7.14-7.54 (m, 15H)	C22H17N3O2	74.35 74.56	4.82 4.98	11.82 11.67

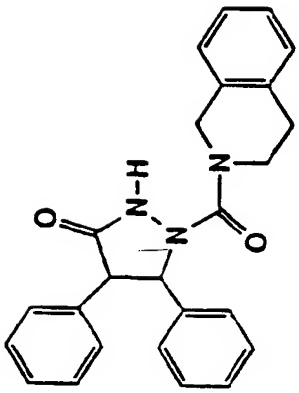


Structure for examples 88-108 below

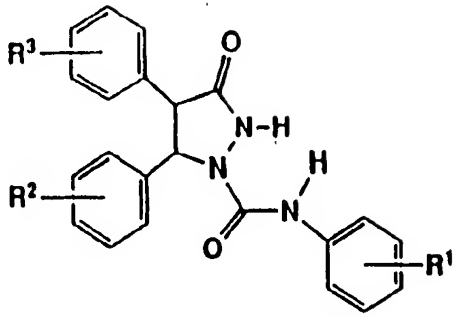
Ex.	R	Method of Prep.	Solvent of Cryst.[a]	Yield, %	Mp. °C	MS	1HNMR	Formula	Analysis, % Theory/Found C	H	N
88	3-Pyridyl	C	precipitated from reaction mixture	3.5 g 73%	208-10	358 (M+)	DMSO 3.8 (s, 1H), 5.54 (s, 1H), 7.27-7.5 (m, 11H), 7.94 (m, 1H), 8.23 (m, 1H), 8.7 (m, 1H), 9.38 (br s, 1H), 10.94 (br s, 1H)	C21H16N4O2	70.38 70.34	5.06 5.16	15.63 15.35
89	4-Pyridyl	C	chrom	183 mg 28%		358 (M+)	CDCl3 3.93 (d, J=6 Hz, 1H), 5.46 (d, J=6 Hz, 1H), 7.18-7.35 (m, 10H), 7.62 (d, J=10 Hz, 2H), 7.95 (d, J=10 Hz, 2H)	C21H16N4O2			
90	1-Naphthyl	A	EtOAc: hexane	790 mg 33%	145-7	407 (M+)	CDCl3 4.03 (d, J=6 Hz, 1H), 5.51 (d, J=6 Hz, 1H), 6.8-7.8 (m, 18H), 9.0 (br s, 1H)	C26H21N3O2	76.64 76.41	5.19 5.33	10.31 10.12
91	2-Naphthyl	A	EtOAc: hexane	1.13 g 44%	172-4	407 (M+)	CDCl3 4.02 (d, J=6 Hz, 1H), 5.60 (d, J=6 Hz, 1H), 7.1-7.9 (m, 18H), 9.38 (br s, 1H)	C26H21N3O2	76.64 76.83	5.19 5.27	10.31 10.26
92	3-Quinolinyl	D	THF: PhMe (came out of reaction mixture)	157 mg 12%	244-6.5	409 (M+)	DMSO 3.81 (s, 1H), 5.57 (s, 1H), 7.29-7.62 (m, 12H), 7.85 (d, J=8 Hz, 1H), 7.91 (d, J=8 Hz, 1H), 8.44 (d, J=2 Hz, 1H), 8.97 (d, J=2 Hz, 1H), 9.62 (br s, 1H), 11.00 (br s, 1H)	C25H20N4O2	73.51 73.48	4.93 4.74	13.71 13.55

Ex.	R	Method of Prep.	Solvent of Cryst.[a]	Yield, %	Mp °C	MS	1HNMR	Formula	Analysis, % Theory/Found C	H	N
93	6-Quinolinyl	D	CH3CN: PhMe	224 mg 32%	222-5	408 (M+)	DMSO 3.79 (s, 1H), 5.58 (s, 1H), 7.25-7.49 (m, 11H), 7.85-7.93 (m, 2H), 8.14 (d, J=1.4 Hz, 1H), 8.20 (d, J=8 Hz, 1H), 8.74 (dd, J=1.4, 4.3 Hz, 1H), 9.45 (br s, 1H), 10.95 (br s, 1H)	C25H20N4O2	73.51 73.88	4.94 5.09	13.72 13.57
94	n-Bu	A	chrom	2.68 g 76%		337 (M+)	DMSO 0.86 (t, J=10 Hz, 3H), 1.15 (m, 2H), 1.38 (m, 2H), 3.08 (m, 2H), 3.62 (s, 1H), 5.47 (s, 1H), 7.18 (s, 1H), 7.3-7.46 (m, 10H), 10.52 (s, 1H)	C20H23N3O2	71.19 71.33	6.87 6.71	12.45 12.27
95	c-Hexyl	A	EtOAc: hexane	1.9 g 83%	152-4	363 (M+)	CDCl3 0.8-1.84 (m, 10H), 3.6 (m, 1H), 3.89 (d, J=6 Hz, 1H), 4.98 (d, J=12 Hz, 1H), 5.42 (d, J=6 Hz, 1H), 7.2-7.45 (m, 10H), 8.66 (s, 1H)	C22H25N3O2	72.70 72.59	6.93 7.03	11.56 11.30
96	CH2Ph	A	chrom	2.6 g 67%		371 (M+)	CDCl3 3.86 (d, J=6 Hz, 1H), 4.31 (dABq, J=8 Hz, Jab=20 Hz, Δv=36 Hz,2H), 5.50 (m, 1H), 5.51 (d, J= 6 Hz, 1H), 7.07-7.43 (m, 16H)	C23H21N3O2	74.37 74.11	5.70 5.77	11.31 11.12
97	CH2Ph (N-Me)	M	chrom (EtOAc: hexane)	380 mg 39%		385 (M+)	CDCl3 2.65 (s, 3H), 3.66 (d, J=2 Hz, 1H), 4.38 (ABq, J=20 Hz, Δv=72 Hz, 2H), 4.94 (d, J=2 Hz, 1H), 6.9 (m, 2H), 7.15-7.46 (m, 13H), 7.9 (br s, 1H)	C24H23N3O2			
98	CH2Ph-2-Cl	M	chrom	149 mg 15%		405 (M+)	CDCl3 3.92 (d, J=7 Hz, 1H), 4.4 (m, 2H), 5.39 (d, J=7 Hz, 1H), 5.55 (t, J=6 Hz, 1H), 7.15-7.43 (m, 14H), 8.48 (br s, 1H)	C23H20ClN3O2	68.06 68.30	4.97 5.13	10.35 10.01
99	CH2Ph-3-Cl	C	EtOAc: hexane	750 mg 29%	133-6	405 (M+)	CDCl3 3.88 (d, J=6 Hz, 1H), 4.26 (dABq, J=7 Hz, Jab=17 Hz, Δv=48 Hz, 2H), 5.48 (d, J=6 Hz, 1H), 5.57 (t, J=7 Hz, 1H), 6.94-7.43 (m, 14H), 8.9 (br s, 1H)	C23H20ClN3O2	68.08 67.78	4.97 5.07	10.35 10.46
100	CH2Ph-4-Cl	A	EtOAc: hexane	182 mg 30%	124-7	405 (M+)	CDCl3 3.89 (d, J=5 Hz, 1H), 4.27 (dABq, J=6 Hz, Jab=12 Hz, Δv= 42 Hz, 2H), 5.48 (t, J=6 Hz, 1H), 5.50 (d, J=5 Hz, 1H), 6.98-7.44 (m, 14H), 8.52 (br s, 1H)	C23H20ClN3O2	68.06 68.22	4.97 5.09	10.35 10.15

Ex.	R	Method of Prep.	Solvent of Cryst.[a]	Yield, %	Mp °C	MS	1HNMR	Formula	Analysis, % Theory/Found C	H	N
101	CH(Me)Ph (S) (1:1 mixture of diastereomers - each optically active)[d]	A	chrom	900 mg 34%		385 (M+)	CDCl3[e] 1.32 (q, J=9 Hz, 3H), 3.90 (dd, J=5 Hz, 9 Hz, 1H), 4.90 (q, J=8 Hz, 1H), 5.37 (dd, J=9 Hz, 38 Hz, 1H), 5.45 (t, J=5 Hz, 1H), 7.0-7.44 (m, 15H), 8.53 (br s, 1H)	C24H23N3O2	74.78 75.04	6.01 6.10	10.90 10.94
102	CH(Me)Ph (R) (1:1 mixture of diastereomers - each optically active)[f]	A	chrom	172 mg 7%		385 (M+)	DMSO[e] 1.20 (t, J=6 Hz, 3H), 3.60 (s, 1/2 H), 3.68 (s, 1/2H), 4.83 (m, 1H), 5.43 (s, 1/2H), 5.52 (s, 1/2H), 7.2-7.55 (m, 15H), 10.58 (s, 1H)	C24H23N3O2			
103	CH(Me)Ph-4-Br (+/-) (single diastereomer obtained in crystallization)[g]	A	EtOAc: hexane	670 mg 33%	145-7	463, 465 (M+'s for Br isotopes)	DMSO 1.41 (d, J=8 Hz, 3H), 3.62 (s, 1H), 4.76 (m, 1H), 5.42 (s, 1H), 7.2-7.62 (m, 15H), 10.56 (s, 1H)	C24H22BrN3O2	62.08 62.27	4.78 4.75	9.05 8.95
104	CH(Me)-1-Naphthyl (R) (c. 3:1 mixture of diastereomers - each optically active)[h]	A	chrom	137 mg 12%		435 (M+)	CDCl3 (peaks for major isomer visible in plot) 1.5 (d, J=9 Hz, 3H), 3.86 (d, J=6 Hz, 1H), 5.48 (d, J=6 Hz, 1H), 5.74 (m, 1H), 7.06-8.19 (m, 19H)	C28H25N3O2			
105	CH2CH2Ph	A	chrom	720 mg 30%		385 (M+)	CDCl3 2.68 (m, 2H), 3.42 (m, 2H), 3.86 (d, J=6 Hz, 1H), 4.94 (t, J=5 Hz, 1H), 5.27 (d, J=6 Hz, 1H), 6.95-7.44 (m, 15H)	C24H23N3O2	74.78 74.49	6.01 6.15	10.90 10.74
106	CH2CH2Ph-2-Cl	C	chrom	2.2 g 63%		419 (M+)	CDCl3 2.82 (m, 2H), 3.45 (m, 2H), 3.85 (d, J=7 Hz, 1H), 5.02 (t, J=6 Hz, 1H), 5.25 (d, J=7 Hz, 1H), 6.95-7.4 (m, 14H), 8.58 (br s, 1H)	C24H22ClN3O2	68.65 68.86	5.28 5.36	10.01 10.01
107	CH2CH2Ph-4-Cl	C	chrom	1.5 g 66%		419 (M+)	CDCl3 2.83 (m, 2H), 3.40 (m, 2H), 3.86 (d, J=8 Hz, 1H), 4.83 (t, J=6 Hz, 1H), 5.22 (d, J=8 Hz, 1H), 6.88-7.42 (m, 14H), 8.45 (br s, 1H)	C24H22ClN3O2	68.65 68.84	5.28 5.36	10.01 9.76
108	CH2CH2CH2Ph	D	chrom (EtOAc: hexane)	239 mg 48%		399 (M+)	CDCl3 1.70 (pentet, J=7 Hz, 2H), 2.48 (t, J=7 Hz, 2H), 3.18 (m, 2H), 3.89 (d, J=6 Hz, 1H), 4.92 (br t, J=6 Hz, 1H), 5.35 (d, J=6 Hz, 1H), 7.02-7.46 (m, 15H), 8.25 (br s, 1H)	C25H25N3O2	75.16 74.89	6.31 6.28	10.52 10.27



Example	Method of Prep.	Solvent of Cryst.[a]	Yield, %	Mp. °C	MS	^{1}H NMR	Formula	Analysis, % Theory/Found C	H	N
109	B	chrom	75 mg 4%	160-6	397 (M+)	CDCl3 2.58-2.82 (m, 2H), 3.37-3.48 (m, 1H), 3.54-3.62 (m, 1H), 3.64 (d, J=2, 1H), 4.37 (d, J=3.5, 2H), 4.95 (d, J=2, 1H), 6.78 (m, 1H), 7.02-7.46 (m, 13H), 8.18 (br s, 1H)	$C_{25}H_{23}N_3O_2$			



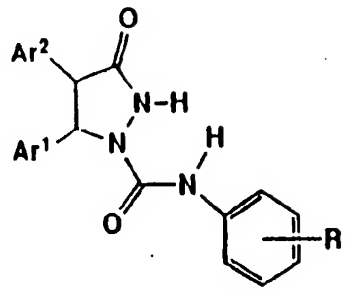
Structure for examples 110-133 below

Ex.	R1	R2	R3	Meth. Prep.	Solvent of Cryst.[a]	Yield, %	Mp, °C	MS	1HNMR	Formula	Analysis, % Theory/Found C	H	N
110	4-CF3	2-Cl	H	A	EtOAc	185 mg 19%		459 (M+)	DMSO 3.57 (br s, 1H), 5.72 (br s, 1H), 7.14-7.82 (m, 13H), 9.72 (br s, 1H), 11.01 (br s, 1H)	C23H17ClF3N3O2	60.07 59.85	3.73 3.80	9.14 8.82
111	4-CF3	3-CN	H	A	triturated with PhMe	1.80g 88%		450 (M+)	DMSO 3.90 (br s, 1H), 5.67 (br s, 1H), 7.12-7.98 (m, 13H), 9.63 (br s, 1H), 10.83 (br s, 1H)	C24H17F3N4O2	64.00 64.09	3.80 3.98	12.44 12.26
112	4-CF3	3-OMe	H	A	chrom (2X with EtOAc: hexane), then triturated with PhMe: hexane	160 mg 9%		455 (M+)	CDCl3 3.82 (s, 3H), 4.03 (d, J=7 Hz, 1H), 5.51 (d, J=7 Hz, 1H), 6.92-7.00 (m, 3H), 7.14-7.50 (m, 10H), ~8.8 (br s, 1H)	C24H20F3N3O3	63.29 63.00	4.43 4.36	9.23 9.03
113	4-CF3	4-N(Me)2	H	A	EtOAc: hexane	95 mg 32%		468 (M+)	DMSO 2.90 (s, 6H), 3.73 (br s, 1H), 5.46 (br s, 1H), 6.77 (d, J=8 Hz, 2H), 7.23-7.40 (m, 7H), 7.62 (d, J=8 Hz, 2H), 7.76 (d, J=8 Hz, 2H), 9.42 (br s, 1H), 10.81 (br s, 1H)	C25H23F3N4O2	64.10 64.26	4.95 5.18	11.96 11.71

Ex.	R1	R2	R3	Meth. Prep.	Solvent of Cryst.[a]	Yield, %	Mp, °C	MS	1HNMR	Formula	Analysis, % Theory/Found C	H	N
114	4-Br	2-Cl	H	A	PhMe, then EtOAc: hexane	47 mg 10%		469, 471 (M+'s for Br isotopes)	DMSO 3.53 (br s, 1H), 5.72 (br s, 1H), 7.12-7.60 (m, 13H), 9.49 (br s, 1H), 10.93 (br s, 1H)	C22H17BrClN3O2	56.13 56.24	3.64 3.62	8.94 8.82
115	4-Br	2-OMe	H	A	EtOAc: hexane	52 mg 17%		465, 467 (M+'s for Br isotopes)	CDCl3 3.72 (s, 1H), 3.78 (s, 3H), 5.50 (br s, 1H), 6.87-7.04 (m, 3H), 7.27-7.52 (m, 10H), 9.29 (br s, 1H)	C23H20BrN3O3	59.24 59.46	4.32 4.23	9.01 8.90
116	4-Br (trans)	2,3-diCl	H	A	triturated with Et2O, then CH2Cl2: hexane (to give CH2Cl2 hemi-solvate)	1.89 g 69%		503, 505 (M+'s), 506, 508 (M+1's for Cl, Br isotopes)	DMSO 3.58 (s, 1H), 5.65 (s, 1H), 5.70 (s, 2H for 1/2 CH2Cl2), 7.28-7.46 (m, 12H), 9.43 (br s, 1H), 10.91 (br s, 1H)	C22H16BrCl2N3O2 •1/2 CH2Cl2	49.35 49.60	3.13 3.25	7.67 7.78
117	4-Br (cis)	2,3-diCl	H	A	CH2Cl2 (2X)	76 mg 54%	198-205	503, 505, 507 (M+'s for Cl, Br isotopes)	DMSO 5.04 (d, J=10 Hz, 1H), 6.30 (m, 1H), 6.72 (d, J=7 Hz, 2H), 7.00-7.12 (m, 3H), 7.30-7.60 (m, 7H), 9.31 (br s, 1H), 10.70 (br s, 1H)	C22H16BrCl2N3O2	52.31 52.59	3.19 3.27	8.32 8.35
118	4-Br	3-CONH2	H	A	CH3CN	237 mg 45%	210-3	479, 481 (M+1's for Br isotopes)	DMSO 3.78 (s, 1H), 5.55 (s, 1H), 7.25-7.59 (m, 12H), 7.80 (d, J=8 Hz, 1H), 7.94 (d, J=24 Hz, 2H), 9.28 (s, 1H), 10.78 (br s, 1H)	C23H19BrN4O3	57.63 57.57	4.00 3.96	11.69 11.66
119	4-Br	4-NO2	H	A	EtOAc: PhMe	343 mg 60%		480, 482 (M+'s for Br isotopes)	DMSO 3.88 (br s, 1H), 5.69 (br s, 1H), 7.30-7.53 (m, 9H), 7.76 (br d, J=7 Hz, 2H), 8.31 (d, J=8 Hz, 2H), 9.39 (br s, 1H), 10.93 (br s, 1H)	C22H17BrN4O4	54.90 55.15	3.56 3.64	11.64 11.55

Ex.	R1	R2	R3	Meth. Prep.	Solvent of Cryst.[a]	Yield, %	Mp, °C	MS	1HNMR	Formula	Analysis, % Theory/Found C	H	N
120	3-CF3, 4-Cl	2-Cl	H	A	EtOAc: hexane	604 mg 44%		493, 495 (M+'s for Br isotopes)	DMSO 3.58 (br s, 1H), 5.72 (br s, 1H), 7.30-7.50 (m, 7H), 7.58-7.67 (m, 3H), 7.93 (d, J=9 Hz, 1H), 8.15 (br s, 1H), 9.83 (br s, 1H), 11.04 (br s, 1H)	C23H16Cl2F3N3O2	55.89 55.85	3.26 3.21	8.50 8.43
121	4-i-Pr	2-Cl	H	A	EtOAc: hexane	514 mg 43%		434 (M+1)	DMSO 1.18 (d, J=7 Hz, 6H), 2.84 (m, J=7 Hz, 1H), 3.51 (br s, 1H), 5.74 (br s, 1H), 7.14-7.64 (m, 13H), 9.27 (br s, 1H), 10.88 (br s, 1H)	C25H24ClN3O2	69.20 69.00	5.58 5.55	9.68 9.73
122	4-Br	H	2-Cl	A	EtOAc	750 mg 43%	182-2.5	470 (M+1)	DMSO 4.16 (br s, 1H), 5.66 (br s, 1H), 7.48-7.88 (m, 13H), 9.56 (br s, 1H), 11.26 (br s, 1H)	C22H17BrClN3O2	56.13 56.35	3.64 3.62	8.93 8.92
123	4-Br	H	3-OMe	A	EtOAc: hexane	520 mg 30%	154-5	467 (M+)	CDCl3 3.72 (s, 3H), 4.94 (d, J=6 Hz, 1H), 5.57 (d, J=6 Hz, 1H), 6.74-6.88 (m, 3H), 7.04-7.32 (m, 7H), 7.42 (br s, 4H), 9.2 (br s, 1H)	C23H20BrN3O3	59.24 59.44	4.32 4.39	9.01 9.06
124	4-Br	H	3-O-i-Pr	A	Et2O: hexane	2.24 g 91%	148-51	493, 495 (M+'s for Br isotopes)	CDCl3 1.22 (t, J=6 Hz, 6H), 3.90 (d, J=4.5 Hz, 1H), 4.43 (septet, J=6 Hz, 1H), 5.58 (d, J=4.5 Hz, 1H), 6.74-6.82 (m, 3H), 7.08 (dd, J=2, 9 Hz, 2H), 7.19-7.29 (m, 5H), 7.36-7.42 (m, 5H)	C25H24BrN3O3	60.74 60.53	4.89 4.94	8.50 8.70
125	4-Br	H	3-NO2	A	CH2Cl2: hexane	1.32 g 48%	150-1.5	480, 482 (M+'s for Br isotopes)	DMSO 4.05 (s, 1H), 5.61 (s, 1H), 7.27-7.52 (m, 9H), 7.66 (t, J=8 Hz, 1H), 7.82 (d, J=8 Hz, 1H), 8.16 (d, J=8, 1H), 8.22 (s, 1H), 9.34 (br s, 1H), 10.95 (br s, 1H)	C22H17BrN4O4	54.90 54.63	3.56 3.67	11.64 11.74
126	4-Br	H	3-Cl	A	EtOAc: hexane	232 mg 27%	142-3	470 (M+1)	CDCl3 4.0 (d, J=6 Hz, 1H), 5.46 (d, J=6 Hz, 1H), 6.87 (br s, 1H), 7.0-7.12 (m, 3H), 7.22-7.54 (m, 10H), 8.78 (br s, 1H)	C22H17BrClN3O2	56.13 56.21	3.64 3.76	8.93 8.84

Ex.	R1	R2	R3	Meth. Prep.	Solvent of Cryst.[a]	Yield, %	Mp, °C	MS	1H NMR	Formula	Analysis, % Theory/Found C	H	N
127	4-Br	H	3-Br	A	chrom, then triturated with Et2O: hexane	128 mg 17%		515, 517 (M+'s), 516 (M+1 for Br Isotopes)	CDCl3 3.94 (br d, J=4 Hz, 1H), 5.46 (br d, J=4 Hz, 1H), 7.04-7.44 (m, 15H)	C22H17Br2N3O2	51.29 51.66	3.33 3.60	8.16 7.88
128	4-Br	H	4-OMe	A	chrom (EtOAc), then triturated with hexane	296 mg 34%		467 (M+)	CDCl3 3.78 (s, 3H), 3.95 (d, J=6 Hz, 1H), 5.49 (d, J=6 Hz, 1H), 6.85 (d, J=12 Hz, 2H), 7.0-7.18 (m, 5H), 7.24-7.5 (m, 7H), 9.1 (br s, 1H)	C23H20BrN3O3	59.24 59.30	4.32 4.53	9.01 8.78
129	4-Br	H	4-Cl	A	triturated with Et2O	1.92 g 82%	172-4.5	469, 471, 473 (M+'s), 470 (M+1 for Cl, Br Isotopes)	DMSO 3.78 (s, 1H), 5.49 (s, 1H), 7.28-7.50 (m, 13H), 9.22 (br s, 1H), 10.84 (br s, 1H)	C22H17ClBrN3O2	56.13 56.03	3.64 3.57	8.93 9.02
130	4-CF3	H	2-Cl	A	triturated with EtOAc: hexane	260 mg 38%	178-9	459 (M+)	CDCl3 4.4 (d, J=6 Hz, 1H), 5.58 (d, J=6 Hz, 1H), 7.2-7.54 (m, 13H), 7.64 (br s, 1H), 9.48 (br s, 1H)	C23H17ClF3N3O2	60.07 60.07	3.73 3.77	9.14 9.18
131	3-CF3, 4-Cl	H	2-Cl	A	triturated with EtOAc: hexane	250 mg 34%	109-10	493 (M+)	CDCl3 4.38 (d, J=6 Hz, 1H), 5.6 (d, J=6 Hz, 1H), 7.16-7.66 (m, 12H), 7.86 (br s, 1H), 9.58 (br s, 1H)	C23H16Cl2F3N3O2	55.89 55.60	3.26 3.24	8.50 8.45
132	4-i-Pr	H	2-Cl	A	EtOAc: hexane	200 mg 31%	226-7	433 (M+)	DMSO 1.16 (d, J=7 Hz, 6H), 2.82 (m, 1H), 3.92 (br s, 1H), 5.46 (br s, 1H), 7.12 (d, J=12 Hz, 2H), 7.28-7.64 (m, 11H), 9.14 (br s, 1H), 10.98 (br s, 1H)	C25H24ClN3O2	69.20 69.45	5.57 5.60	9.68 9.68
133	4-Br	2-Cl	2-Cl	A	EtOAc: hexane	4.32 g, 88%		505 (M+)	DMSO 4.02 (br s, 1H), 5.75 (br s, 1H), 7.28-7.58 (m, 12H), 9.41 (br s, 1H), 11.06 (br s, 1H)	C22H16BrCl2N3O2	52.30 52.07	3.19 3.27	8.32 8.09



Ex.	R	Ar1	Ar2	Meth. Prep.	Solvent of Cryst.[a]	Yield, %	Mp. °C	MS	1H NMR	Formula	Analysis, % Theory/Found C	H	N
134	4-Br	Ph	1-Naphthyl	A	Et2O: hexane	1.48 g 61%	187-9	486, 488 (M+1's for Br isotopes)	CDCl3 4.70 (d, J=6 Hz, 1H), 5.59 (d, J=6 Hz, 1H), 6.97 (d, J=9 Hz, 2H), 7.15-7.52 (m, 12H), 7.70-7.88 (m, 3H), 9.10 (br s, 1H)	C26H20BrN3O2	64.21 64.02	4.15 4.20	8.64 8.61
135	4-Br	3-Pyridyl	Ph	A	EtOAc (2X), then chrom, then EtOAc	848 mg 24%	184-87.5	437, 439 (M+1's for Br isotopes)	DMSO 3.84 (s, 1H), 5.56 (s, 1H), 7.23-7.46 (m, 10H), 7.83 (d, J=8 Hz, 1H), 8.53 (dd, J=1.1, 4.5 Hz, 1H), 8.65 (d, J=1.7 Hz, 1H), 9.28 (s, 1H), 10.86 (br s, 1H)	C21H17BrN4O2	57.68 57.74	3.92 3.99	12.81 13.07

a Includes other methods of purification such as chromatography (chrom), trituration, and precipitation, as indicated. If only solvents are given, compound was purified by recrystallization from those solvents. For other methods of purification, solvents used follow in parentheses.

b After recrystallization from EtOAc:hexane.

c Purified by extraction into 1N NaOH, followed by acidification with 1N HCl and extraction into organic solvent (Et2O or EtOAc). Evaporation of solvent gave material homogeneous by TLC and of satisfactory purity.

d Prepared using S-(-)-α-methylbenzylisocyanate.

e All splitting patterns reported are those apparent upon visual inspection of plot, and reflect a combination of true proton-proton magnetic couplings, and multiplicity due to presence of a mixture of two diasteromers.

f Prepared using R-(+)-α-methylbenzylisocyanate.

g Prepared using (±) 4 bromo-α-methylbenzylisocyanate.

h Prepared using (R) (-)-1-(1-Naphthyl)ethylisocyante.

Test Procedures for CCK And Gastrin Receptor Binding (IC_{50})

Brain

Brain CCK receptor binding was performed using mouse brain membranes according to the method of Chang and Lotti (Proc. Natl. Acad. Sci. 83: 4923-4926, 1986). Male CF-1 mice, 23-25 g were sacrificed by cervical dislocation, the forebrain removed and placed in ice cold 50 mM Tris buffer, pH 7.4. The tissue was homogenized in 100 volumes of the Tris buffer with a Brinkman Polytron or Tekmar Tissumizer and then centrifuged at 40,000 g for 10 min. Pellets were resuspended in Tris buffer, centrifuged as above and then resuspended in 100 volumes of assay buffer, pH 6.5 (20 mM N-2-hydroxyethyl-piperazine-N'-2-ethane sulfonic acid (HEPES), 1 mM ethylene glycol bis(2-aminoethyl ether-N,N,N',N'-tetraacetic acid) (EGTA), 5 mM $MgCl_2$, 130 mM NaCl, and 0.25 mg/ml bacitracin). The binding assay consisted of 50 µL of compound (or buffer for total binding), 50 µL of ^{125}I-CCK-8 sulfate (20 pM) (Amersham IM-159), 200 µL of assay buffer and 200 µL of homogenate (80-120 µg protein). The samples were incubated at room temperature (25°) for 2 hours, and they were then filtered through GF/B glass fiber filters (soaked in wash buffer for 2 hours before use) using a 48 well Brandel cell harvester designed for receptor binding. The filters were washed twice with 3 ml of 50 mM Tris buffer, pH 7.4, containing 0.01% BSA and then counted for radioactivity in plastic tubes with a Micromedic 10/600 automatic gamma counter.

Compounds were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 10 mM and then further diluted with assay buffer. The concentration of DMSO in the incubation was 0.1% or less and had no effect on the assay at that level. IC-50 values of displacement curves were determined using 7 concentrations of compound and were calculated using the ALLFIT computer program of DeLean, Munson and Rodbard (Am. J. Physiol. 235: E97-E102, 1978). Non-specific binding was determined as the displacement of the radioligand by 100 nM CCK-8 sulfate.

Pancreas

Binding to peripheral type CCK receptors in rat pancreas was done according to the method of Chang et al. (Mol. Pharmacol. 30: 212-217, 1986) using ^{3}H-L364, 718. Pancreas was obtained from male Sprague-Dawley rats, 150-200 g, after decapitation, and dissected free from adipose and connective tissue. The tissue was homogenized in 30 volumes of 50 mM Tris buffer, pH 7.4 and centrifuged at 40,000 g for 10 min. The tissue pellet was washed by resuspension and centrifugation as described above. The final pellet was suspended in 500 volumes of assay buffer (50 mM Tris buffer, pH 7.4, 5 mM $MgCl_2$, 0.14 mg/ml bacitracin, and 5 mM dithiothreitol) to give a protein concentration of 30-60 µg/200 µl. Reagent volumes for the assay were the same as those used for CCK binding to brain membranes. Tritium labeled L-364,718 (Dupont NEN, NET-971) was used as the ligand at a concentration of 0.4-0.6 nM. The samples were incubated 1 hour at room temperature and then filtered as described for the CCK-brain receptor. Scintillation cocktail was added to the filters which were counted for radioactivity using a Micromedic Taurus automatic liquid scintillation counter.

Compound samples were prepared and IC-50 values were determined as described for the CCK-brain experiments. Non-specific binding was that amount left bound to the filters after adding 100 nM L-364,718.

Gastric Mucosa

The method used for gastrin binding to guinea pig stomach mucosal membranes was similar to that described by Takeuchi, Speir and Johnson (Am. J. Physiol. 237(3): E284-E294, 1979). Guinea pig stomach fundus was obtained from male Hartley guinea pigs, 300-350 g, and the mucosa was scraped off with a glass slide. The mucosa was homogenized in 50 mM Tris buffer, pH 7.4, containing 1 mM phenylmethanesulfonyl fluoride using a Dounce glass homogenizer, and the suspension was centrifuged at 40,000 g for 10 min. The resulting pellet was resuspended and centrifuged once more, the final pellet was then suspended in 100 ml assay buffer per 1 guinea pig stomach to give a protein concentration of 200-300 µg/200 µl. The assay buffer consisted of 50 mM Tris buffer, pH 7.4, 5 mM $MgCl_2$, 0.14 mg/ml bacitracin, and 1 µg/ml each of leupeptin, chymostatin, aprotinin and pepstatin. Reagent volumes for the assay were the same as those used for CCK binding to brain membranes. The radioactive ligand was 20 pM ^{125}I-gastrin I, from DuPont NEN (NEX-176). The samples were incubated 3 hours at room temperature and filtered and counted as described for CCK binding to brain membranes. Compound samples were prepared and IC-50 values were determined as described for the CCK-brain receptor binding. Non-specific binding was determined using 100 nM gastrin I (human synthetic from Sigma Chemical Co.).

Table II below summarizes representative CCK and gastrin-binding tests results for exemplified com-

pounds in accordance with this invention.

TABLE II

CCK and Gastrin Receptor Binding Data

Compound of Example No.	IC_{50}, μM, or Percent Inhibition (at 1 or 10 μM)		
	Brain	Pancreas	Gastrin
1	0.022	0.19	0.15
2	0.29	14(10)	
3	0.054	34(10)	1.1
4	0.39	78(10)	
5	77(10)	18(10)	
6	4.4	15(10)	
7	1.1	81(10)	
8	34(10)	2(10)	
9	3.7	33(10)	
10	57(10)	4(10)	
11	67(10)		
12	0.34 (O-)	64(10)	
	1.9 (N-)	55(10)	
13	67(10)		
14	2.6	60(10)	
15	69(10)	10(10)	
16	0.044	62(10)	0.42
17	0.52	6(10)	
18	0.093	22(10)	
19	68(10)	36(10)	
20	0.031	11.6	0.49
21	0.057	77(10)	
22	42(1)	27(10)	
23	0.49	23(10)	

TABLE II (continued)
CCK and Gastrin Receptor Binding Data

Compound of Example No.	IC_{50}, μM, or Percent Inhibition (at 1 or 10 μM)		
	Brain	Pancreas	Gastrin
24	0.15	45(10)	
25	0.21	14(10)	
26	0.075	47(10)	
27	0.23	60(10)	
28	0.44	55(10)	
29	0.025	47(10)	0.26
30	0.031	49(10)	0.35
31	54(1)	71(10)	
32	42(1)	69(10)	
33	0.34	20(10)	
34	1.5	12(10)	
35	0.39	48(10)	
36	0.45	33(10)	
37	82(1)	75(10)	
38	0.056	53(10)	0.24
39	0.33	52(10)	
40	0.75	38(10)	
41	57(10)	21(10)	
42	0.78	37(10)	
43	0.23	24(10)	
44	0.26	67(10)	
45	0.022	0.16	
46	0.042	1.2	0.21
47	0.39	51(10)	
48	0.080	98(10)	
49	0.043	40(10)	0.25
50	0.013	87(10)	0.081
51	18(1)	25(10)	
52	60(1)	21(10)	
53	1.2	17(10)	
54	1.15	53(10)	
55	0.60	47(10)	
56	25(1)	15(10)	
57	1.0	45(10)	
58	10(1)	85(10)	
59	44(1)	75(10)	
60	34(10)	37(10)	
61	56(10)	78(10)	

TABLE II (continued)
CCK and Gastrin Receptor Binding Data

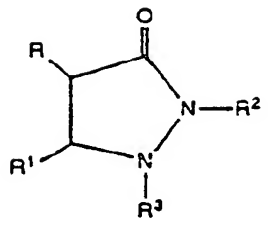
Compound of Example No.	IC_{50}, μM, or Percent Inhibition (at 1 or 10 μM)		
	Brain	Pancreas	Gastrin
62	2.2	37(10)	
63	0.51	0.075	
64	5.3	34(1)	
65	50(10)	37(10)	
66	40(10)	23(10)	
67	46(10)		
68	4.3	70(10)	
69	0.5	12(10)	
70	13(1)	36(10)	
71	1.2	39(10)	
72	88(10)	22(10)	
73	16(10)	20(10)	
74	23(10)	15(10)	
75	60(10)	40(10)	
76	55(10)	4(10)	
77	56(10)	20(10)	
78	1.8	49(10)	
79	43(10)	9(10)	
80	5.2	9(10)	
81	95(10)	59(10)	
82	23(10)		
83	37(1)	12(10)	
84	70(10)	26(10)	
85	78(10)	19(10)	
86	1.1	58(10)	
87	47(10)	23(10)	
88	40(10)	37(10)	
89	34(10)	21(10)	
90	45(1)	63(10)	
91	0.010	94(10)	0.062
92	0.064	88(10)	0.16
93	0.29	75(10)	0.66
94	50(10)		
95	55(10)	18(10)	
96	42(10)	13(10)	
97	42(10)		
98	74(10)	33(10)	
99	3.3	86(10)	

TABLE II (continued)
CCK and Gastrin Receptor Binding Data

Compound of Example No.	IC_{50}, μM, or Percent Inhibition (at 1 or 10 μM)		
	Brain	Pancreas	Gastrin
100	2.2	78(10)	
101	1.3	7(10)	
102	4.7	11(10)	
103	0.87	78(10)	
104	0.9	47(10)	
105	0.49	43(10)	
106	0.19	78(10)	0.87
107	86(10)	61(10)	
108	1.3	87(10)	
109	6.0	11(10)	
110	0.007	47(10)	0.13
111	0.020	35(10)	0.61
112	0.072	42(10)	1.4
113	25(1)	21(10)	
114	0.020	38(10)	0.36
115	0.15	53(10)	0.32
116	0.031	80(10)	0.23
117	0.40	64(10)	1.0
118	0.36	41(10)	5.2
119	1.2	64(10)	
120	0.016	87(10)	0.12
121	0.014	26(10)	0.12
122	0.015	8.6	0.22
123	0.068	23(10)	0.69
124	0.15	36(10)	0.73
125	0.10	42(10)	0.59
126	0.011	59(10)	0.21
127	0.032	73(10)	0.21
128	0.49	39(10)	
129	0.16	69(10)	0.86
130	0.012	42(10)	0.10
131	0.012	61(10)	0.062
132	0.008	48(10)	0.070
133	0.006	7.9	0.025
134	0.033	75(10)	0.093
135	0.14	18(10)	1.7

Claims

1. A compound of the formula



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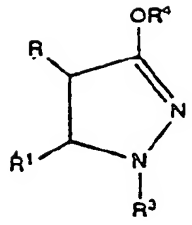
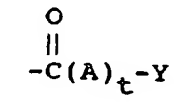
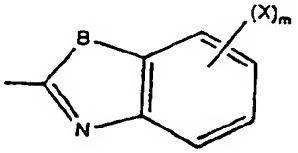


I II

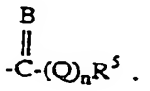
wherein R and R^1 are independently hydrogen, C_1-C_6 alkyl, phenyl, benzyl, naphthyl, pyridyl or substituted phenyl having 1, 2, or 3 substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halo, trifluoromethyl, phenyl, phenoxy, phenyl(C_1-C_4 alkyl), phenyl(C_1-C_4 alkoxy), phenylacetyl, C_1-C_6 alkanoyl, cyano, carbamyl, nitro, C_1-C_6 alkoxycarbonyl, methylenedioxy, C_3-C_6 alkylene, amino, -NH(C_1-C_4 alkyl or benzyl), and N(C_1-C_4 alkyl)$_2$;
R_2 is hydrogen, C_1-C_6 alkyl, carboxymethyl, C_1-C_4 alkoxycarbonylmethyl or a group of the formula



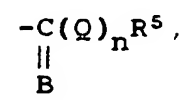
wherein t is 1 or 0; A is -CH_2-, -O-, -NH- or -N(C_1-C_6 alkyl)-; and Y is phenyl or substituted phenyl as defined above;
R_4 is C_1-C_6 alkyl, carboxymethyl, or C_1-C_4 alkoxycarbonylmethyl;
R_3 is hydrogen or a group of the formula



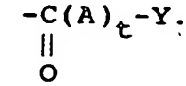
or



wherein B is O or S; X is selected from the phenyl substituents defined above; m is 0, 1 or 2; n is 0 or 1; Q is -NH-, -N(C_1-C_6 alkyl)-, -S-, or -O-; and R^5 is a group of the formula -[CH(R^6)]$_q$-(CH_2)$_r$-R^7 wherein R^6 is hydrogen or C_1-C_6 alkyl; q is 0 or 1; r is 0, 1 or 2; and R^7 is hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, pentafluorophenyl, pyridyl, tetrahydronaphthyl, indolyl, quinolinyl, phenyl, naphthyl, or phenyl or naphthyl substituted with 1, 2, or 3 substituents as defined above for phenyl; or the group -$(Q)_nR^5$ is 2-tetrahydroisoquinolinyl; and the pharmaceutically acceptable salts thereof;
provided that at least one of the groups R or R^1 is other than hydrogen or C_1-C_6 alkyl, and R or R^1 is hydrogen only when the other of R and R^1 is substituted phenyl in which the substituent is phenyl; and provided further that at least one of the groups R_2 and R_3 is other than hydrogen, and when R^3 is a group of the formula



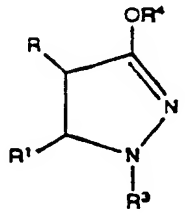
R^2 is other than a group of the formula



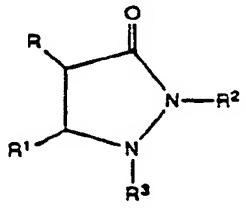
2. A compound as claimed in Claim 1 wherein R and R^1 are in the trans stereoconfiguration.

3. A compound as claim d in Claim 1 wherein R and R^1 are in the cis stereoconfiguration.

4. A compound as claimed in any one of Claims 1 to 3 having the formula



5. A compound as claimed in any one of Claims 1 to 3 having the formula



6. A compound as claimed in Claim 5 wherein R^2 is a group of the formula -CONHY.

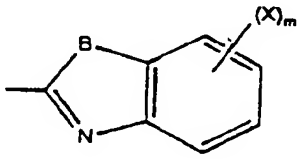
7. A compound as claimed in any one of Claims 1 to 6 wherein R^3 is hydrogen.

8. A compound as claimed in any one of Claims 1 to 6 wherein R^2 is methyl or carboxymethyl.

9. A compound as claimed in any one of Claims 1 to 8 wherein R and R^1 are phenyl or substituted phenyl.

10. A compound as claimed in any one of Claims 1 to 5 wherein R^2 is hydrogen.

11. A compound as claimed in Claim 10 wherein R_3 is a group of the formula



12. A compound as claimed in Claim 10 or 11 wherein R and R^1 are phenyl.

13. A compound as claimed in any one of Claims 10 to 12 wherein B is S.

14. A compound as claimed in any one of Claims 10 to 12 wherein B is 0.

15. A compound as claimed in any one of Claims 10 and 12 to 14 wherein R^3 is a group $-CB(Q)_n-(CH(R^6)]_q-(CH_2)_r-R^7$.

16. A compound as claimed in Claim 15 wherein R^3 is $-CSNH-(CH(R^6)]_q-(CH_2)_r-R^7$.

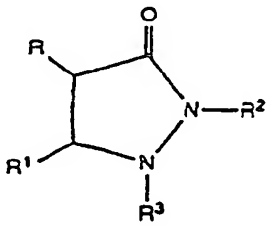
17. A Compound as claimed in claim 15 or 16, wherein q and r are 0 and R^7 is phenyl or substituted phenyl.

18. A compound as claimed in any one of Claims 15 to 17, wherein R and R^1 are phenyl or substituted phenyl.

19. A pharmaceutical formulation comprising as an active ingredient an effective amount of a compound of any one of Claims 1 to 18 and a pharmaceutically acceptable carrier, excipient or diluent therefor.

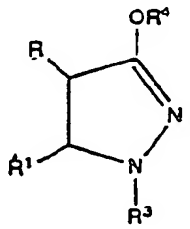
Claims for the following Contracting States : GR and ES

1. A pharmaceutical formulation comprising, as an active ingredient, a compound of the formula



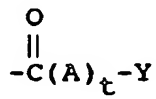
I

or

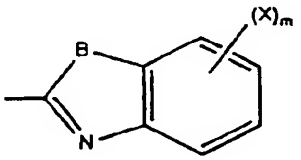


II

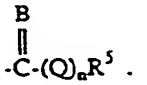
wherein R and R^1 are independently hydrogen, C_1-C_6 alkyl, phenyl, benzyl, naphthyl, pyridyl or substituted phenyl having 1, 2, or 3 substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halo, trifluoromethyl, phenyl, phenoxy, phenyl (C_1-C_4 alkyl), phenyl(C_1-C_4 alkoxy), phenylacetyl, C_1-C_6 alkanoyl, cyano, carbamyl, nitro, C_1-C_6 alkoxy-carbonyl, methylenedioxy, C_3-C_6 alkylene, amino, -NH(C_1-C_4 alkyl or benzyl), and N(C_1-C_4 alkyl)$_2$;
R_2 is hydrogen, C_1-C_6 alkyl, carboxymethyl, C_1-C_4 alkoxycarbonylmethyl or a group of the formula



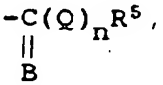
wherein t is 1 or 0; A is -CH_2-, -O-, -NH- or -N(C_1-C_6 alkyl)-; and Y is phenyl or substituted phenyl as defined above;
R_4 is C_1-C_6 alkyl, carboxymethyl, or C_1-C_4 alkoxycarbonylmethyl;
R_3 is hydrogen or a group of the formula



or



wherein B is O or S; X is selected from the phenyl substituents defined above; m is 0, 1 or 2; n is 0 or 1; Q is -NH-, -N(C_1-C_6 alkyl)-, -S-, or -O-; and R^5 is a group of the formula -[$CH(R^6)]_q$-$(CH_2)_r$-R^7 wherein R^6 is hydrogen or C_1-C_6 alkyl; q is 0 or 1; r is 0, 1 or 2; and R^7 is hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, pentafluorophenyl, pyridyl, tetrahydronaphthyl, indolyl, quinolinyl, phenyl, naphthyl, or phenyl or naphthyl substituted with 1, 2, or 3 substituents as defined above for phenyl; or the group -$(Q)_nR^5$ is 2-tetrahydroisoquinolinyl; and the pharmaceutically acceptable salts thereof;
provided that at least one of the groups R or R^1 is other than hydrogen or C_1-C_6 alkyl, and R or R^1 is hydrogen only when the other of R and R^1 is substituted phenyl in which the substituent is phenyl; and provided further that at least one of the groups R_2 and R_3 is other than hydrogen, and when R^3 is a group of the formula



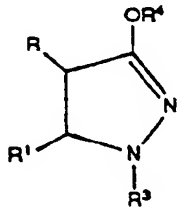
R^2 is other than a group of the formula

$$-C(A)_t-Y.$$
$$\|$$
$$O$$

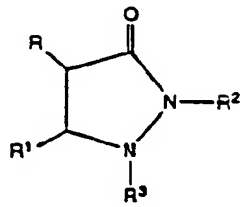
2. A formulation as claimed in Claim 1 wherein R and R^1 are in the trans stereoconfiguration.

3. A formulation as claimed in Claim 1 wherein R and R^1 are in the cis stereoconfiguration.

4. A formulation as claimed in any one of Claims 1 to 3 having the formula



5. A formulation as claimed in any one of Claims 1 to 3 having the formula



6. A formulation as claimed in Claim 5 wherein R^2 is a group of the formula -CONHY.

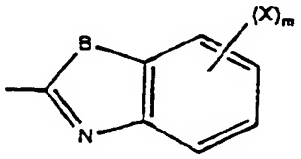
7. A formulation as claimed in any one of Claims 1 to 6 wherein R^3 is hydrogen.

8. A formulation as claimed in any one of Claims 1 to 6 wherein R^2 is methyl or carboxymethyl.

9. A formulation as claimed in any one of Claims 1 to 8 wherein R and R^1 are phenyl or substituted phenyl.

10. A formulation as claimed in any one of Claims 1 to 5 wherein R^2 is hydrogen.

11. A formulation as claimed in Claim 10 wherein R_3 is a group of the formula



12. A formulation as claimed in Claim 10 or 11 wherein R and R^1 are phenyl.

13. A formulation as claimed in any one of Claims 10 to 12 wh rein B is S.

14. A formulation as claimed in any one of Claims 10 to 12 wherein B is 0.

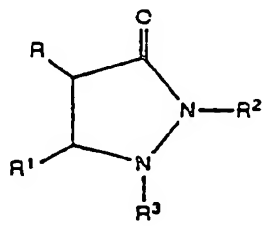
15. A formulation as claimed in any one of Claims 10 and 12 to 14 wherein R^3 is a group $-CB(Q)_n-[CH(R^6)]_q-(CH_2)_r-R^7$.

16. A formulation as claimed in claim 15 wherein R^3 is $-CSNH-[CH(R^6)]_q-(CH_2)_r-R^7$.

17. A formulation as claimed in Claim 15 or 16, wherein q and r are 0 and R^7 is phenyl or substituted phenyl.

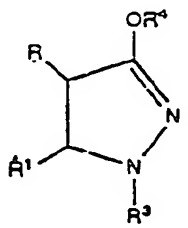
18. A formulation as claimed in any one of Claims 15 to 17, wherein R and R^1 are phenyl or substituted phenyl.

19. A process for producing a compound of the formula



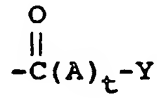
I

or

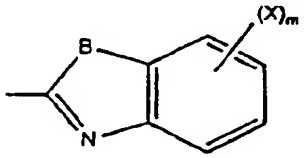


II

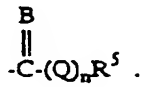
wherein R and R^1 are independently hydrogen, C_1-C_6 alkyl, phenyl, benzyl, naphthyl, pyridyl or substituted phenyl having 1, 2, or 3 substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halo, trifluoromethyl, phenyl, phenoxy, phenyl(C_1-C_4 alkyl), phenyl(C_1-C_4 alkoxy), phenylacetyl, C_1-C_6 alkanoyl, cyano, carbamyl, nitro, C_1-C_6 alkoxy-carbonyl, methylenedioxy, C_3-C_6 alkylene, amino, -NH(C_1-C_4 alkyl or benzyl), and N(C_1-C_4 alkyl)$_2$;
R_2 is hydrogen, C_1-C_6 alkyl, carboxymethyl, C_1-C_4 alkoxycarbonylmethyl or a group of the formula



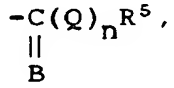
wherein t is 1 or 0; A is $-CH_2-$, -O-, -NH- or -N(C_1-C_6 alkyl)-; and Y is phenyl or substituted phenyl as defined above;
R_4 is C_1-C_6 alkyl, carboxymethyl, or C_1-C_4 alkoxycarbonylmethyl;
R_3 is hydrogen or a group of the formula



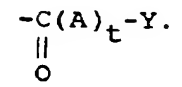
or



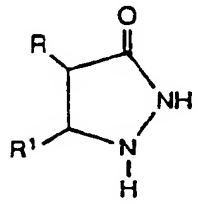
wherein B is O or S; X is selected from the phenyl substituents defined above; m is 0, 1 or 2; n is 0 or 1; Q is -NH-, -N(C_1-C_6 alkyl)-, -S-, or -O-; and R^5 is a group of the formula $-[CH(R^6)]_q-(CH_2)_r-R^7$ wherein R^6 is hydrogen or C_1-C_6 alkyl; q is 0 or 1; r is 0, 1 or 2; and R^7 is hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, pentafluorophenyl, pyridyl, tetrahydronaphthyl, indolyl, quinolinyl, phenyl, naphthyl, or phenyl or naphthyl substituted with 1, 2, or 3 substituents as defined above for phenyl; or the group $-(Q)_nR^5$ is 2-tetrahydroisoquinolinyl; and the pharmaceutically acceptable salts thereof;
provided that at least one of the groups R or R^1 is other than hydrogen or C_1-C_6 alkyl, and R or R^1 is hydrogen only when the other of R and R^1 is substituted phenyl in which the substituent is phenyl; and provided further that at least one of the groups R_2 and R_3 is other than hydrogen, and when R^3 is a group of the formula



R^2 is other than a group of the formula



which comprises acylating or alkylating a 3pyrazolidinone of the formula

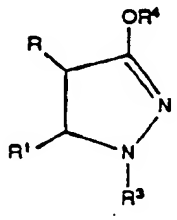


under neutral or basic conditions with an acylating or alkylating agent selected to give the desired compound.

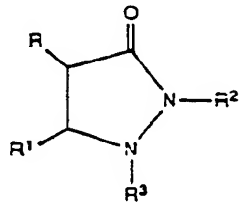
20. A process as claimed in Claim 19 wherein R and R^1 are in the trans stereoconfiguration.

21. A process as claimed in Claim 19 wherein R and R^1 are in the cis stereoconfiguration.

22. A process as claimed in any one of Claims 19 to 21 having the formula



23. A process as claimed in any one of Claims 19 to 21 having the formula



24. A process as claimed in Claim 23 wherein R^2 is a group of the formula -CONHY.

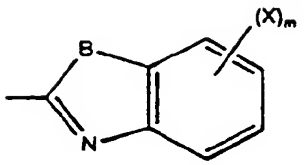
25. A process as claimed in any one of Claims 19 to 24 wherein R^3 is hydrogen.

26. A process as claimed in any one of Claims 19 to 24 wherein R^2 is methyl or carboxymethyl.

27. A process as claimed in any one of Claims 19 to 26 wherein R and R^1 are phenyl or substituted phenyl.

28. A process as claimed in any one of Claims 19 to 23 wherein R^2 is hydrogen.

29. A process as claimed in Claim 28 wherein R_3 is a group of the formula



30. A process as claimed in Claim 28 or 29 wherein R and R^1 are phenyl.

31. A process as claimed in any one of Claims 28 to 30 wherein B is S.

32. A process as claimed in any one of Claims 28 to 30 wherein B is 0.

33. A process as claimed in any one of Claims 28 and 30 to 32 wherein R^3 is a group $-CB(Q)_n-[CH(R^6)]_q-(CH_2)_r-R^7$.

34. A process as claimed in Claim 33 wherein R^3 is $-CSNH-[CH(R^6)]_q-(CH_2)_r-R^7$.

35. A process as claimed in Claim 33 or 34, wherein q and r are 0 and R^7 is phenyl or substituted phenyl.

36. A process as claimed in any one of Claims 33 to 35, wherein R and R^1 are phenyl or substituted phenyl.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 30 6374

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	FR-A-2 529 786 (ETABLISSEMENTS NATIVELLE S.A.)		C07D231/08 A61K31/415 C07D401/04 C07D401/06 C07D403/06 C07D413/04 C07D417/04 A61K31/44 A61K31/47 A61K31/40 A61K31/42 A61K31/425
A	EP-A-0 155 523 (A.NATTERMANN & CIE.GMBH)		
A	EP-A-0 373 512 (MITSUI TOATSU CHEMICALS, INC.)		
A	FR-A-1 114 874 (KODAK-PATHE)		
A	FR-E-82 186 (KODAK-PATHE)		
D,A	EP-A-0 166 355 (MERCK & CO.INC.)		

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07D
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	30 OCTOBER 1991	DE BUYSER I.A.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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